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PAEDIATRICS IN DENMARK

DEVELOPMENT AND STATUS

By OLUF ANDERSEN

Paediatrics in Denmark is relatively of recent date, the first lectureship in paediatrics at the University of Copenhagen having been established in 1892 and the first chair in 1931. For many years the study of for subject was optional; in 1912 it was made obligatory, the medical students, was introduced but compulsory examination not until 1936, the first examination being held in 1939. Since then paediatrics has formed a natural part of the medical curriculum at the universities of Copenhagen and Aarhus.

Notwithstanding its relatively short life in Denmark, paediatrics has developed considerably and now occupies a firmly established position among the branches of Danish medical science. I shall try quite briefly to sketch the course followed by this development.

The first children's hospital in Denmark was founded on private means in 1850 in Riegensgade, Copenhagen. It had only 12 beds and soon proved to be too small.

However, funds were obtained by means of public collections and it was possible to build a new and larger hospital. It was opened on June 16, 1879, under the name of "Dronning Louises Børnehospital" (Queen Louise's Children's Hospital), Her Majesty Queen Louise becoming its first patroness.

The hospital comprised five departments with a total of 60 beds. Today, after several extensions have been made, there is accommodation for 174 patients counting those at the country ward.

It was not until 1910 that the next important progress in paediatrics on the hospital system came, when the Paediatric Department at the Rigshospital was opened. This was an event comparable in significance to the founding of the first children's hospital, because now the University acquired its own children's department, signifying that it had taken the first step along the path leading to the recognition of paediatrics as an independent and important branch of medicine.

Later, in 1917, the Municipality of Copenhagen opened its first children's hospital, Børnehospitalet at Fuglebakken. Since then a number of children's department have been set up in and out of Copenhagen, so that Denmark now has a total of 12 paediatric departments with more than 900 beds, and another will be opened in about a year's time.

Besides these hospital departments there are several outpatient clinics for children's diseases, for example at the Rigshospital and Dronning Louises Børnehospital.

Until the founding of the Dronning Louises Børnehospital, instruction in paediatrics was in the hands of the professors of obstetrics. With the new hospital, instruction in paediatrics became possible on a broader basis and its first physician-in-chief, Professor Harald Hirschsprung, 1892, was appointed lecturer in paediatrics, a post that was subsequently assumed by his successors at the hospital.

When the University acquired its own paediatric clinic at the Rigshospital in 1910, instruction naturally became centered there under Professor C. E. Bloch. As already stated, in 1912 paediatrics became an obligatory subject of the medical faculty, but Bloch was not appointed full professor until 1931.

While instruction in paediatrics was assuming a more regular form, scientific paediatric research made its appearance. Professor Harald Hirschsprung (b. 1830, d. 1916) became world renowned for his description of megacolon congenitum *(Hirschsprung's disease)*. Among other works that made him famous mention may

be made of his fundamental studies of stenosis pylori congenita and the bloodless reposition of intestinal intussusceptions.

His successor, Svenn Monrad, earned well-deserved merit by the publication of his excellent lectures "Pædiatriske Forelæsninger og Studier", 1903, and later "De vigtigste Mave-Tarmsygdomme i den første Barnealder", 1928. Mention must also be made of his works on the tuberculin test on children ("Monrad's plaster test", mistakenly called "Moro"s plaster test) and those on epilepsy and intestinal intussusception. In 1917—18, C. E. Bloch by his work on xerophthalmia gave clinical proof that this affection is due to a vitamin-A deficiency; a Japanese work on the same subject was not known at that time. Also of great importance was Bloch's work on diseases of intestinal canal, in which gastroenteritis was recognized as an intestinal infection.

In 1917—18 Carl Friderichsen described acute adrenal cortex insufficiency, the *Friderichsen-Waterhouse syndrome*. Assisted by K. A. Jensen, Valdemar Poulsen made the first systematic studies of gastric lavage in children. This work, published in 1928, became of great importance to the diagnostics of tuberculosis.

Going into greater detail would be beyond the scope of this article, but I might mention some more examples of recent literature in order to illustrate how paediatrics spans over many fields. There are patho-anatomical, clinical and social-paediatric works such as Boesens & Vendel: investigations on 1100 cases of congenital heart diseases; P. Plum & H. Dyggve: works on vitamin K deficiency; the neurological works of Sv. Brandt, especially encephalographic studies; J. Øster: Mongolism; H. Debes Joensen: studies on the frequency and importance of nursing; and Vagn Christensen: Housing conditions and child morbidity.

In the course of time paediatricians have had to devote themselves to central problems of various kinds.

At the beginning of this present century mortality in the first post-natal year was high: in 1901 it was 13.4 per cent of all live-born children. The chief-causes of death were gastro-intestinal diseases and infections of the respiratory tract.

With the improving standard of living and the consequent better hygiene and nutrition, as well as improved treatment of the sick and an improved prophylaxis, it has gradually become possible to combat morbidity among infants, especially the gastrointestinal affections, so that they now play a much more subordinate role than before. At the same time, after the discovery of antibiotics and chemotherapeutics, the mortality of pneumonia has dropped very heavily. As a result, mortality in the first post-natal year has decreased, until now — in 1955 — it is 2.5 per cent.

These improved conditions have naturally set their mark upon paediatrics. The first paediatricians in Denmark from the beginning of the century, Hirschsprung, Monrad, and Bloch, regarded the combating of infant mortality as their all-important task. Therefore, a large proportion of their scientific work and instruction was concerned with the problems of infancy. With the falling mortality, paediatricians had more chance of occupying themselves with other aspects of the science.

Another development which made this possible was the fact that more and more paediatric departments were being opened, whereby the work could be more widely distributed.

Whereas in the early days of paediatrics the work — apart from studies on infantile diseases — was somewhat fragmentary if not actually incidental, nowadays in the various departments it has become concentrated in particular special branches: while the children's departments fulfill the function of general paediatric hospitals, they have become specialized in one field or another.

Specialization has been an imperative factor in the work of keeping abreast of the great advances made in paeditrics. Nowadays it is quite impossible for one chief physician to keep up with all the special fields within the branch. In all probability it will be necessary to carry specialization even further. At the same time the fact must not be lost sight of that it would be unfortunate if specialization were carried to such extremes that the various special departments were segregated from the general paediatric departments. Paediatrics ought to remain a unity, in which the various special elements are no more than well-bordered facets to break the monotony.

Side by side with the hospital work in Denmark there has been a great amount of prophylactic work done among children. A survey of the development and present stage of that work appears in this issue of the Bulletin.

I cannot conclude this brief review of paediatrics and its branches in Denmark without referring to the great influence of the Danish Paediatry Societic on this section of medicine.

The Society was started on October 13, 1908, on the initiative of Professor Svenn Monrad. The scientific works read at the monthly meetings have gone far to elevate the standard of science within paediatrics in Denmark.

Moreover, the Society has done important work to promote co-operation with the rest of Scandinavia, a cooperation which led to the founding in 1919 of the Scandinavian Paediatric Society, which arranges a Scandinavian congress every other year, the publication of "Acta Paediatrica", which first appeared in 1921, and the issue of a joint Scandinavian textbook of paediatrics.

PREVENTIVE MEDICAL CARE OF CHILDREN IN DENMARK

By RICHARD FRIEDBERG and FOLKE TUDVAD

The social and health measures taken in Denmark for the protection of the population, including the children especially, should properly be seen on the background of certain facts concerning the country and its people.

The Kingdom of Denmark, covering about 44,000 sq. kilometres, has a population of about 4.3 million, with agriculture and industry as its chief source of livelihood. Practically half the people live in the rural areas, about a quarter in the capital and the other quarter in the provincial towns. The age distribution is:

under 1 year	78,000
1—6 years	515,000
7—14 »	535,000
15—65 »	2,763,000
over 65 »	390,000

About 80,000 children are born every year, and the annual number of deaths in the aggregate population is about 40,000.

Up to about a hundred years ago it was the custom in Denmark, as elsewhere, for the family, the employer and the church to care for the poor or the sick. The subsequent industrial and economic developments made these relief measures inadequate with the result that the State and the local authorities became more and more involved in the care of the needy. This new system was put in statute form in the Act of the Constitution of 1849, which on this subject states that anyone unable to earn a living has a right to public assistance. Since then the relief and health measures in Denmark have been constantly extended by both State and Communes.

Present day legislation dealing with the social and health measures in Denmark covers the entire population. Within this legislative complex are a number of enactments dealing particularly with children. It is not within the scope of the present review to describe the social measures in detail, and it will therefore be restricted to those health measures that have been taken for the protection of sick and healthy children.

For almost three quarters of a century Denmark has had a sick-club system based upon mutual insurance, in recent years supplemented by State grants. Subject to a certain maximum income limit, this arrangement ensures a constantly expanding section of the people free hospital treatment, free general and special medical attention and inexpensive medicines. Nowadays about 85 per cent of the population are included in this system; it applies only to the age groups from 14 years and upwards, but the children are insured collectively with their parents.

Sick children in all parts of the country can be treated in general hospital departments, but in addition there are a number of special departments for the treatment of children's diseases.

One group of children suffering from certain ailments comes under a system of special care which is financed by the State: spastics, epileptics, mental defectives, cripples, blind, deaf and those with defective speech. Through the medium of a compulsory system of notifications the community ensures that discovery is made at the earliest possible moment of all children suffering from affections requiring treatment, institutional care, training or reschooling.

Now that infant mortality and morbidity have been fought with such success, society has its hands free to concentrate more upon the task of preserving the health of the healthy. In Denmark this course of events has led to Acts of Parliament prescribing preventive measures from prenatal life to the termination of a child's schooldays.

By the *Pregnancy Hygiene Act*, all expectant mothers are granted the right to a number of examinations by midwife and doctor during pregnancy and immediately after childbirth. This right is taken advantage of by about 75 per cent of the pregnant women. At these examinations a check-up is made of the mother's state of health and the foetal development, a Wassermann test is made and, when considered necessary, a Rhesus group determination. One result to which these examinations have contributed is that cases of fresh congenital lues no longer occur in Denmark.

About seventeen years ago the legislature established a *Maternity Aid Institution*, with branches at many places throughout the country. At that institution every pregnant woman and every mother can obtain personal, social and legal support, advice and guidance, free of charge. For example, since its establishment the institution has helped to bring encouragement to many expectant mothers in difficult circumstances and put them in a position to go through with their pregnancy. The Maternity Aid Institution, however, is not content merely to guide and advise; it has facilities for providing material support, both in the form of a place to stay during and after pregnancy and in the form of outfits for mother and child.

Through the sick-club system the expectant mother is ensured free midwife and medical assistance during and immediately after confinement. This help is of great importance in Den-

mark, where about half the births take place at home. In the case of confinements in hospital or special maternity departments, however, free assistance is given to single mothers, mothers from poor homes and also in cases where there is a likelihood of complicated delivery. A small number of births take place in private maternity homes, the patients paying only for their board and lodging while the sick-clubs defray the cost of the obstetric and medical assistance. When a mother is confined in her own home she can have home help and a nurse.

For women who have an occupation outside the home, the sick-club rules and a special statute provide for monetary assistance for a fortnight before and up to a month after childbirth. There is no particular legislation with general provisions for ensuring that such women can keep their jobs at such times, but most labour agreements are so framed as to provide for them so that they retain their job and their full pay or a part of it.

All women who are entitled to be members of sick-clubs have a right to a daily half litre of milk free during the last six months of pregnancy, and after childbirth to a whole litre daily during the child's first six months if she looks after it herself.

For the past twenty years Denmark has had an *Act for the prevention of morbidity and mortality among children in the first post-natal year.* Under this Act the various local governing bodies may appoint specially trained nurses (health nurses) who, after notification by the midwife of the birth of a child, call on the mother a few days later and offer their assistance. If the mother accepts — only one or two per cent decline it — the nurse will normally pay from nine to twelve visits to the home during the child's first year, advising the mother on feeding and nursing matters, watching the child's progress and recommending the various prophylactic medical examinations and vaccinations to which the child has a right. These nurses never treat sick children, their duty being to see that they come under the attention of the family doctor.

Besides the supervision of these specially trained health nurses, the *Medical Examination of Children Act* provides for free examinations at the ages of 5 weeks, 5 months, 10 months, 15 months, 2 years, 3 years, 4 years, 5 years and 6 years, nine examinations in all. They may be given by the family doctor or at special stations managed by trained paediatrists, and comprise a general clinical overhaul to enable the physician to appraise the child's somatic and psychical development. The mother is advised as to the child's feeding, nursing, hygiene and upbringing and as to the preventive measures (vaccinations) to which the child is entitled. Should these examinations uncover a morbid condition, the child comes under the treatment of the family doctor.

On their own initiative a number of communes and private enterprises have opened various forms of day nurseries where solitary breadwinners or married couples who both go out to work can place their children for the half or whole day. These institutions are intended to help the family, for in addition to feeding and caring for the children they assist in occupying and educating them. Most of them are under regular medical supervision. Commune and State may contribute up to 70 per cent of the running expenses, the parents paying according to their means.

Should it happen that a child temporarily cannot be looked after at home — perhaps because its mother is ill — it can be placed in an approved home for a time.

The *School Medical Act* aims at health and hygiene at the schools. All school children are medically examined once a year, also for tuberculosis; they are measured and weighed, their sight and hearing are tested and their general hygiene inspected. For children who have difficulty in keeping up with the rest of the class, for instance owing to defective sight or hearing, or lack of ability, etc., the school doctor advises with regard to having them placed in special classes. He gives no treatment except in emergencies, sick children otherwise being referred to their own doctor. The school doctor also acts in an advisory capacity to the authorities and teaching personnel as to school hygiene. He is assisted by school health nurses who, when necessary, pay visits to the children's homes.

At the Copenhagen schools and some others outside the capital there are dental clinics, where the children have their teeth inspected regularly and also treated if need be.

Any local authority may provide free meals for children at school in the winter period from November to April, but only in the first six years of their schooling. The food may either be in form of a meal or a half pint of milk with a vitamin supplement.

For school children whose parents go out to work a number of communes have opened recreation centres for the purpose of occupying children outside of school hours and helping them with their preparation.

Private institutions and schools have started recreation homes and rural colonies, where children in need of country air can be sent, usually for periods of one to three months.

All these measures aim, chiefly on a voluntary basis, at providing the best possible chances of development for children from normal homes. But the community has been particularly anxious to make provision for children from bad homes and those exposed to neglect.

The relevant measures are more coercive in character and may be limited to supervision of

the homes or, in grave cases, may involve removing the children from their parents. As there is always a chance of arbitrary decisions in these often very serious matters, parents or guardians have the right to appeal against such public measures to the courts.

Apart from the Acts of Parliament described, intended for supervising and preserving the health of the young by means of physical examinations and parental guidance, the State works more actively by offering them free vaccination for diphtheria (+ tetanus), polio, tuberculosis and smallpox. The first three are optional to the parents, but smallpox vaccination is compulsory by law.

The health authorities recommend giving the three diphtheria-tetanus vaccinations at the age of 5, 6 and 18 months, so that vaccination begins with the doctor's prophylactic examination when the child is five months old. In the towns the offer of vaccination has been utilized for between 80 and 90 per cent of the children.

Polio vaccination, which is intracutaneous, commences with the health examination at the age of 10 months, the last two injections being given at 11 and 22 months. It should be added that this year the authorities have offered polio vaccination free to everybody under the age of 40.

BCG vaccination for children is not bound to any fixed period, being dependent — in infancy and later — upon environment and state of health. At any rate, all tuberculin-negative children are offered BCG vaccination when they begin school. In Copenhagen about a fourth of the children are vaccinated in infancy or when very young and about half will have been vaccinated when they leave school. However, these figures cannot be taken as the average for the whole country, because there are considerably lower and higher vaccination frequencies in the various provincial areas.

Smallpox vaccination, unlike all other forms of immunization, is compulsory as already stated, and the Act was issued about eighty-five years ago. Parents are advised to have their children vaccinated before the age of 2 years.

The administration of these prophylactic statutes, like that of most Danish public health measures, is decentralized in form, being in the hands of the local authorities (the communes). The cost of the School Medical Service is defrayed by the State, while State and communes together pay what it costs to carry out the others. The Danish National Health Service, which is the country's highest health authority, supervises the observance of the laws and receives reports from the various institutions concerned with their carrying out in practice.

A special committee appointed by the Home Office correlates the administrative and scientific work carried out according to the legislation mentioned.

CHILD MORBIDITY IN A GOOD AND A BAD RESIDENTIAL AREA

By VAGN CHRISTENSEN

Within the past few decades the view has been gaining ground that the morbidity of a population is to be regarded as a function of the structure in the widest sense of this population. This view is readily accepted when comparing, for instance, the morbidity in a so-called underdeveloped country with that in a Western-European population, having to a great extent formed the basis of the hygienic and therapeutic measures taken to improve the state of public health in underdeveloped countries.

The same point of view is far more difficult to maintain where the morbidity in one's own community is concerned. The housing problem seems to be a good example of this. Several investigations have been made within the past 70 years into the significance of this environmental factor. It seems, however, as if the experience gained thereby has been utilized only to a small extent in the hygienic education of the medical profession, and consequently even less in that of the population.

The results of previous studies on the relation between housing conditions and health are in several respects so unanimous that we may be justified in regarding them as facts:

1) Using morbidity or mortality as a hygienic measure, man is susceptible to bad housing conditions from birth. The susceptibility increases to a maximum at the age of 2 or 3 years, then to decline at a slower rate, being hardly demonstrable about the age of 10 years. However, in the cases of a few groups of a population (e. g. mothers) and a few diseases (e. g. tuberculosis) adults also seem to have a higher morbidity and mortality under bad housing conditions.

2) The difference in morbidity and mortality is due in the main to infectious diseases among children, especially bronchitis, pneumonia, measles, pertussis, meningitis and acute dyspepsia. Other diseases show varying differences (e. g., prematurity, congenital malformations, and others).

be of hygienic importance, such as the size, the number of persons per room and the quality of the house.

3) Certain properties of the dwelling seem to

4) Differences in morbidity and mortality between separate residential groups are also found within groups of population with uniform incomes or of the same social class.

Such results were reported by Carnally et al. 1887, Chalmers 1913, Brownlee 1918, 1922 and 1925, Woodbury 1925, Rietz 1930, Stocks 1934, Joensen 1949 and 1954, Stein 1950 and 1952, as well as Spence et al. 1954, among others. For further details reference is made to a review of the literature stated elsewhere (Vagn Christensen 1956).

MATERIAL

A comparison has been made between the admissions to hospital of children from two distinct residential areas of Copenhagen.

Residential areas: 1) About 10,000 flats situated in the oldest and worst slum quarters, examined and assessed with regard to quality by the Municipal House Inspection and Condemnation Board with a view to possible condemnation.

2) The district of Emdrup, a fairly new and hygienically satisfactory residential area comprising approximately the same number of persons.

Children: All children under 7 years of age in the stated residential areas, counted at the census in 1950, grouped according to size of dwelling and quality of house.

Hospitalized children: Admissions within the period of 1948—1952 of children under 7 years of age. The material was collected from so many Copenhagen hospital units that practically all admissions of children from the examined areas must be supposed to have been included in the investigation. Excluded were children admitted to surgical departments.

RESULTS

Table 1 gives a survey of the materials from the two areas examined. It is seen that at the time of investigation there lived 2844 children under 7 years of age in the area examined by the Municipal House Inspection and Condemnation Board (below called the "Board area"). Of these, 1484 had been in hospital once or more within the stated period, the total number of admissions amounting to 2169.

Table 1.

Number of children, number of admissions and number of children admitted from the areas examined. Number of admissions and number of admitted children per 1000 children in each area, for the period of 1948—1952 and annually.

	Board area	Emdrup
Number of children	2844	2236
Number of admissions	2169	813
Number of children admitted ..	1484	599
per 1000 children in each area:		
Number of admissions	763	364
Number of admitted children ..	522	269
Number of admissions annually	153	73

At Emdrup there lived 2236 children under 7 years of age. Of these 599 had been in hospital within the period of investigation, the total number of admission being 813.

The figures have been made comparable by calculating the number of admissions per 1000 children in each area. It is seen that per 1000 children in the Board area 522 had been admitted to hospital within the period of investigation, while at Emdrup the corresponding figure was 269. The 522 children from the Board area had been admitted altogether 763 times, and the 269 from Emdrup altogether 364 times. The annual admission rate from the Board area was about 15 per cent and that from Emdrup about 7 per cent.

Thus, the admission rate was twice as high from the Board area as from Emdrup, both as regards the number of hospitalized children and as regards the total number of admissions. For practical reasons the number of admissions will be employed below.

Table 2 shows the age incidences in the two areas. The number of children living in each area and the number of hospitalized children have been grouped according to age. The admission rate per 100 children in each age group in each area has been calculated on this basis, partly for the whole period and partly annually.

It is seen that in the Board area about 35 per cent annually were admitted within the first year of life, and 24 per cent within the second year, while during the following years the annual admission rate fell steadily to about 7 per cent at the age of 5 or 6 years. At Emdrup the corresponding figures were 16, about 10 and about 5 per cent respectively. During the first 2 or 3 years the admission rate was thus 2 to 2.5 times higher from the Board area than from Emdrup. From the age of 4 years the admission rate from the Board area was 1.5 to 1.8 times higher than that from Emdrup. The age distribution of children admitted from a bad residential area differs, in other words, somewhat from that of children admitted from a good area. It is seen, for instance, that of the children admitted from the Board area about one-third were under 1 year old, about one-third 1 to 3, and about one-third over 3 years old. From Emdrup the admissions within the first year of life amounted to less than one-fourth of the total number of admissions and those in the age-class of 1 to 3 years to a scant one-third, while about half of the admitted were over 3 years old.

Table 3 illustrates the frequencies of the various diagnoses in the hospital materials from the two areas. Conversion has been made to number per

Table 2.

Age incidence: number of children in each area and number of admissions grouped according to age. Admissions in each age group per 100 children of the same age-class in the area, for the whole period and annually. The ratio of B. a./E. calculated for each age-class.

age	Board area childr.	adms.	adms. per. 1000 childr. 1948-52 annually	Emdrup childr.	adms.	adms. per 1000 childr. 1948-52 annually	B.a./E.
0—1 year	412	725	176	35.2	227	179	79	15.8	2.2
1—2 years	358	428	120	24	242	115	48	9.6	2.5
2—3 "	385	287	75	15	272	114	42	8.4	1.8
3—4 "	456	254	56	11.2	338	126	37	7.4	1.5
4—5 "	417	182	44	8.8	384	111	29	5.8	1.5
5—6 "	419	149	36	7.2	404	84	21	4.2	1.7
6—7 "	397	143	36	7.2	369	84	23	4.6	1.6
Total	2844	2169	76	15.2	2236	813	36	7.2	2.1

1000 children in each area, and the ratio between the two areas has been calculated for each diagnosis. The diagnoses set out in the table constitute the total number stated in the case reports concerned. No distinction has been made between primary and secondary diseases.

It is seen that the admission rates from the two areas differed very considerably in various groups of diseases. Within the group of respiratory diseases the upper respiratory affections and asthma caused twice as many admissions from the Board area as from Emdrup, while bronchitis, pneumonia and otitis media caused 3 or 4 times as many admissions from the bad residential area as from the good. These differences in admission rate probably indicate corresponding differences in morbidity, so that the figures must be taken as evidence that the ordinary upper respiratory diseases tend to run a severer and more complicated course in children living under bad housing conditions. The incidences of tuberculosis seemed to be equal in the two areas, a surprising result compared with those of other investigations (Stein 1950 and 1952). The figures here arrived at may be due to a more extensive B. C. G. vaccination in the bad residential area (Vagn Christensen 1956).

Meningitis showed an excess of admissions from the bad area of the same order as pneumonia and bronchitis. The absolute figures are relatively

Table 3.

Frequencies of various diagnoses in the two hospital materials, stated in absolute figures and per 1000 children in each area. The ratio of B. a./E. for each disease.

diagnoses	Board area abs.	per 1000	Emdrup abs.	per 1000	Total	B.a./E.
Ac. upper respiratory diseases	664	233	256	114	920	2.0
Chr. " " "	439	154	212	94	651	1.6
Pneumonia, bronchitis	385	135	74	33	446	3
Otitis media	351	123	95	42	459	4.1
Tuberculosis	30	11	24	11	54	1
Asthma, asthmat. bronchitis	68	24	26	12	94	2
Meningitis	29	10	6	2.7	35	3.7
Poliomyelitis	37	13	29	13	66	1
Scarlet fever	93	33	52	23	145	1.4
Measles	101	35	22	10	123	3.5
Pertussis	99	35	22	10	121	3.5
Infectious skin diseases	78	27	7	3	85	9
Non-infectious " "	129	45	20	9	149	5
Burns	35	12	8	3.6	43	3.3
Ac. dyspepsia	259	91	52	23	311	4
Chr. "	23	8	8	3.6	31	2.2
Constipation	35	12	11	5	46	2.4
Other gastro-intestinal diseases	60	21	29	13	89	1.6
Prematurity	81	28	30	13	111	2.2
Cong. debility a. o.	23	8	8	3.5	31	2.3
Cong. malformations	72	25	25	11	97	2.3
Abd. colic, tic a. o.	124	44	94	42	218	1
Enuresis, encopresis	64	22	24	11	88	2
Maladjustment	115	40	73	33	188	1.2
Convulsions	63	22	48	21	111	1
Oligophrenia	36	13	21	9	57	1.4
Anaemia	287	101	91	41	278	2.5
Rickets	47	17	16	7	63	2.4

small, but they are of interest, because all cases of meningitis must be supposed to be admitted to hospital, so that we may here take it that differences with regard to admission represent differences in morbidity.

The numbers of admissions due to poliomyelitis were almost equal when comparing the total groups of children under 7 years of age. Examinations of the individual age-classes separately revealed, however, a higher admission rate from the bad than from the good residential area for the youngest age-classes, while the reverse was the case for the age-class of 4—7 years.

Regarding children's diseases, the number of children admitted with measles and pertussis was 3 or 4 times greater from the Board area than from Emdrup, whereas no significant difference was noted for scarlet fever. These figures are in accord with those found by previous investigators (Brownlee 1925, Strøm 1939, and others).

Skin diseases, both infectious and non-infectious, showed very pronounced differences, the admission rates from the bad residential area being 5 to 9 times as high as from the good. The number of children admitted with burns was 3 times greater from the Board area than from Emdrup.

Admissions due to acute gastro-intestinal diseases were about 4 times as frequent from the Board area as from Emdrup, and admissions due to other gastro-intestinal diseases about twice as frequent. A similar excess of admissions from the Board area was found for prematurity, congenital malformations and congenital debility, enuresis, encopresis, anaemia and rickets.

It is seen that in the groups of presumably nervous disorders, maladjustment, convulsions and oligophrenia no particular difference was found between the two areas. These results are difficult to assess, because the problems and symptoms leading to admission probably differ in different environments. We may presumably be justified in concluding that the figures do not suggest any particular differences with regard to hereditary predispositions between the two groups of population here compared.

Summarizing, we may say about the differences found in the present study as regards the incidences of various diseases under different housing conditions that

1) one group occurred with almost the same frequency in the two series (scarlet fever, tuberculosis, oligophrenia, convulsions, nervous disorders),

2) one group was about twice as frequent in the Board area as at Emdrup. It seems reasonable to relate this distribution to the inferior conditions in general met with in bad residential areas (as regards nutrition, care, hygiene, etc.), where the housing also plays a part, but is unlikely to be the sole unfavourable environmental factor of importance. These factors seem to have a very extensive effect (anaemia, rickets, enuresis, encopresis, gastro-intestinal diseases, prematurity, congenital malformations, upper respiratory diseases, etc.).

3) Finally, for one group of diseases the admission rate was about 4 times (or more) higher from the bad residential area than from the good. To this group belong infectious diseases, including acute gastro-intestinal diseases, skin diseases, as well as burns, i. e., diseases whose spread and courses may reasonably be supposed to depend in some measure on crowding in damp and dark rooms with little sunlight coming in. It seems justifiable to regard the housing as a factor playing a direct part in the distribution within this group of diseases.

Table 4.

Number admitted from the two areas by incidence and period of breast-feeding. Absolute figures and per 1000 admissions in each area. Frequency in the Board area expressed in per cent of that at Emdrup.

	Board area abs	Board area per 1000	Emdrup abs	Emdrup per 1000	B.a./E. x 100
Not stated....	759	350	265	327	107
No breast-feeding	340	157	114	140	112
Breast-feeding commenced ..	991	457	410	505	90
After 1 month remain	651	301	321	394	77
After 2 months remain	424	196	259	320	61
After 3 months remain	259	119	175	215	55
After 4 months remain	178	82	139	171	48
After 5 months remain	146	67	112	138	49
After 6 months remain	79	37	57	70	53
Breast-feeding until adms. ..	79	37	24	29	128
Total of admissions	2169	1000	813	1000	

The material was examined with a view to the difference between the two areas in the individual age groups (Vagn Christensen 1956). With the stated exception (poliomyelitis), the difference between the admissions from the two areas was of approximately the same order in the various age groups, the admissions within the first years of life being quantitatively of by far the greatest importance, however.

Table 4 shows the incidences of breast-feeding in the two groups of hospitalized children. In about one-third of the cases no information regarding breast-feeding could be procured from the hospital unit concerned. These cases being equally distributed between the two series, the figures have nevertheless been thought useful, though no definite conclusions could be drawn from them.

Table 5.

Material from death certificates: Number of births and number of dead under 1 year of age in the two areas within the period of investigation. Deaths grouped according to diagnoses, expressed in absolute figures and per 1000 births. The ratio of B.a./E.

	Board area abs.	Board area per 1000	Emdrup abs.	Emdrup per 1000	Total	B.a./E.
Births 1948—1952	1925		1236			
Dead under 1 year 1948—52	81	42	26	21	107	2
of these with						
Prematurity, cong. debilit., cong. malformations etc.	89	46	32	26	121	1.8
Infectious diseases	35	18	36	25	41	3.6
Other diseases	2	1	2	2	4	—

It is seen that about 10 per cent more of the children admitted from the Board area than of those admitted from Emdrup had not been breast-fed. Of those who had started with breast-feeding 10 to 15 per cent more had ceased within each of the first 3 months of life in the Board area than at Emdrup, so that after the age of 3 or 4 months breast-feeding had been twice as frequent in the hospital material from Emdrup as in that from the Board area.

These figures might be conceived to have resulted from a particularly high admission rate for artificially nourished children; but such proved not to be the case. The table shows that of infants breast-fed until admission there were 37 per 1000 admissions in the Board area and 29 at Emdrup. As 1000 admissions from the Board area corresponded to 1300 children in the area (cf. Table 1), whereas 1000 admissions from Emdrup corresponded to about 2800 children, calculation of the number of admitted breast-fed children in proportion to the number of children in each area showed the admission rate for this group, too, to be twice as high from the Board area as from Emdrup.

Hence, there is hardly any doubt that the differences found with regard to breast-feeding between the series of hospitalized children from the two areas represent similar differences between the total groups of children in these areas.

Comparison of the Two Areas by Other Methods of Examination.

The question whether the admission rate can be regarded as an indication of the morbidity in each of the areas examined is of decisive importance in assessing the results achieved. A few supplementary investigations were therefore carried out to clarify this question.

The material was procured by reviewing the death certificates from the period of investigation. It thus comprised all infants dead under 1 year of age (including those dead at home). (Table 5). It is seen that the total infant mortality in the Board area was twice as high as that at Emdrup. In the group of diseases of the newborn 1.8 times as many had died in the Board area as at Emdrup, and in the group of infectious diseases 3.6 times as many. These results are in close accordance with those found in the hospital materials.

Table 6 illustrates the results of home visits for the purpose of seeking information on the number of children with proper diseases treated at home. As proper diseases were regarded protracted and/or recurrent throat infections, otitis media, bronchitis, pneumonia, and the like. Some cases of cold running an uncomplicated course were not included. The morbidity rate was figured out on the basis of the number of children for whom information was available on the stated morbidity. The results were compared with the admission rate in the corresponding residential group.

Table 6.

Comparison of admissions to hospital and morbidity in the home in the same residential group.

	Board area	Emdrup	B.a./E.
Number of families examined	106	72	
Number of children under 7.	162	88	
Per 100 children:			
Admissions 1948—1952	69	22	3
Number with morbidity at home	72	8	9

This comparison gave the result that the admission rate by no means gave a fully reliable picture of the morbidity actually found in the bad residential area. The admission rate from the bad residential area was 3 times as high as that from the good; but the number of children with proper diseases treated at home was 9 times greater in the bad area.

DISCUSSION

A comparison of two series of hospitalized children admitted from a good and a bad residential area respectively revealed very great quantitative as well as qualitative differences. As stated in the section dealing with diagnoses, there seems to exist a group of diseases the occurrence of which may reasonably be supposed, on a physiological basis, to be a direct effect of bad housing conditions. However, this factor, too, can be differentiated in various components.

The housing conditions compared in the present study comprise at least three components:

1) The quarter. This can in part be expressed numerically by means of the density of population (number of persons per hectare = a scant half acre). This was in the Board area 300—900 and at Emdrup 50—100.

2) The size of the dwelling: More than two-thirds of the examined children from the Board area lived in one- and two-room dwellings, and the rest in larger dwellings. Of those admitted from Emdrup, about half lived in two-room dwellings, hardly any in one room, and the rest in larger dwellings.

3) The quality of the house: Just over one-third of the children from the Board area lived in condemnable houses, about one-third in sanitarily unsatisfactory houses, which, though improvable, are definitely of an inferior quality from a hygienic point of view, and about one-third in satisfactory houses. At Emdrup practically all houses are satisfactory.

As shown elsewhere (Vagn Christensen 1956), the significance of each of these components of the housing factor was demonstrable in the material here presented. The comparison made has thus served to illustrate the total effect of these properties of the dwelling.

Numerous other environmental factors will be found to differ when comparing such two residential groups, a close relationship existing between income and social position on one hand and the housing conditions on the other. These relations doubtless played an essential part in some of the results acheived, but seem by no means to account for the differences found. On the contrary, groups with a low income and an inferior social position seem to have an increased admission rate only if the housing conditions are also bad (Vagn Christensen 1956).

SUMMARY

The investigation showed a considerable difference between the admission rate from a good residential area and that from a bad:

1) The admission rate was about twice as high from the bad area as from the good.

2) The difference was due in the main to a particularly high admission rate from the bad residential area among infants within the first years of life.

3) The excess of admissions from the bad area was not of the same order for all groups of diagnoses. Some diseases (e. g. scarlet fever, tuberculosis and oligophrenia) were equally represented, while others were twice as frequent from the bad residential area as from the good (e. g., upper respiratory infections, anaemia and prematurity), and one group, especially infectious diseases, was 3 or 4 times more frequent in the bad residential area. The latter group was probably directly related t othe housing conditions.

4) Breast-feeding was less common in the bad residential area than in the good, but this could not account for the difference with regard to admissions.

5) The results achieved by comparing the two series of hospitalized children were in close accordance with those of a corresponding mortality analysis, but did not express the full difference between the areas with regard to morbidity in the homes.

It is stated that certain properties of the dwelling played a part in the comparison here reported, and that the significance of each could be differentiated. Other environmental factors were likewise involved, but could hardly explain the results.

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CEREBRAL PALSY

A CLINICAL SURVEY OF 543 CASES

by P. PLUM

The present series comprises all cases of cerebral palsy examined, and, in the majority of cases, treated in The University Clinic of Paediatrics, Rigshospitalet, Copenhagen, during the years 1949—May 1956. During the same period 240 children suffering from other organic nervous conditions were examined. These are not included in this study, their being classified in the following diagnostic groups: mental deficiency with slight neurological symptoms (60), epilepsy without signs of cerebral palsy (45), retarded motor development without signs of cerebral palsy (56), progressive muscular dystrophy (20), Werdnig Hoffmann's disease (9), cerebral tumour, Duchenne-Erb's paresis (6), and, finally, a group of children with aphasia, defects of coordination, and slight neurological symptoms which cannot be classified as typical cases of cerebral palsy (44).

In all cases, examination and treatment were undertaken by the author. Examination of the eyes and X-ray examination of the cranium and hips were performed routinely. Air encephalography was performed in 208 cases and electroencephalography in 383 cases. The majority of the patients have been examined at regular intervals throughout several years and still attend for outpatient treatment.

The distribution of the case material appears from Table 1, Table 2, and Fig. 1.

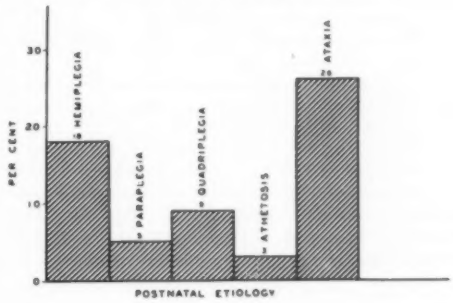

Fig. 1.
Percentage of Postnatally Acquired Cases in Each Diagnostic Group.

The fact that the cases of quadriplegia constitute such a great percentage of the total material is due to the circumstance that The University Clinic of Paediatrics has admitted a relatively large proportion of the most severely affected patients because, on principle, no child suffering from cerebral palsy is refused.

From The University Clinic of Paediatrics, Rigshospitalet, Copenhagen.

Table 1.
Distribution of Cases According to Diagnosis, Natal or Postnatal Etiology, Age, and Sex.

	Age in Years				Sex		
	0—3	4—7	8—14	15 and more	Boys	Girls	Total No.
Hemiplegia, congenital	28	19	33	7	47	40	87
Hemiplegia, postnatally acquired	5	8	5	1	8	11	19
Paraplegia, congenital	20	36	26	9	48	43	91
Paraplegia, postnatally acquired	0	1	4	0	5	0	5
Quadriplegia, congenital	102	54	33	13	94	108	202
Quadriplegia, postnatally acquired	11	2	4	4	12	9	21
Athetosis: Icterus gravis, blood incompatibility	12	12	2	0	14	12	26
Athetosis: Icterus gravis, no blood incompatibility	10	9	5	2	13	13	26
Athetosis: Icterus gravis, blood incompatibility not examined	4	2	2	1	6	3	9
Athetosis: No pronounced neonatal icterus	9	8	8	3	22	6	28
Athetosis: Postnatally acquired	1	1	1	0	1	2	3
Ataxia, congenital	2	7	5	0	6	8	14
Ataxia, postnatally acquired	2	1	2	0	0	5	5
Monoplegia, congenital	2	2	0	0	1	3	4
Triplegia, congenital	2	0	0	0	1	1	2
Torsion spasm	0	0	1	0	1	0	1
Total No.	210	162	131	40	279	264	543

Table 2.
Distribution of 92 Cases, Diagnosed as "Athetosis".

		No. of Cases	Asphyxia at Birth No.	Abnormalities of Labour No.	Birth Weight < 2500 g No.	Athetosis No.	Boys No.	Girls No.
Icterus neonat. gravis.	Rh-immunization	20	4	5	2	17	11	9
	A-immunization	6	1	0	3	6	3	3
	No immunization	26	9	13	13	17	13	13
	Immunization not examined	9	1	3	5	5	6	3
	Total	61					33	28
Light neonatal icterus		3	0	2	2	3	2	1
No neonatal icterus		23	17	11	6	23	18	5
	Total	26					20	6
Insufficient neonatal data		2	—	—		2	2	0
Postnatally acquired		3	0	1		3	1	2

Incidence of cerebral palsy in the family, of other organic nervous disease in the family and of symptoms during pregnancy appear from Table 3.

In Table 3, the group of cases which developed post-natally is included for comparison. It will be observed that *familial incidence (and heredity)* do not appear to play any numerically significant rôle. Similarly, the incidence of other organic nervous disease in the family appears to be uniformly distributed throughout the groups with the exception of the group of ataxia in which the incidence is twice that in the other groups. Although the number of patients with ataxia is small, the greater incidence of organic nervous conditions in the family must, however, be considered to agree with the conception that ataxia is frequently due to a hereditary trait.

Toxaemia of *pregnancy* and haemorrhage appear to be of a certain etiological importance, perhaps directly but more probably indirectly by their effect on the delivery. Pathological conditions in pregnancy do not appear to play any rôle of numerical significance. The heading "miscellaneous" includes common symptoms such as injuries to the abdomen, oedema of the ankles, mental shock, pyelitis, cystitis, biliary colic, etc. These

Table 3.
Incidence of Cerebral Palsy in the Family, Incidence of Other Organic Nervous Diseases in the Family and Incidence of Symptoms during Pregnancy.

		Hemiplegia congenital		Paraplegia congenital		Quadriplegia congenital		Athetosis congenital		Ataxia congenital	Postnatally Acquired	
		No.	%	No.	%	No.	%	No.	%	No.	No.	%
Cerebral Palsy in Family		4	0	6**	7	6*	3	4*	5	0	2	4
Other Organic Nervouse Disease in Family		19	23	21	23	44	22	17	19	8	15	28
Pregnancy	Nausea and Vomiting	20	24	22	24	31	15	25	28	2	12	23
	Toxaemia	3	4	2	2	5	2	1	1	0	0	0
	Haemorrhage	9	11	10	11	12	6	7	8	2	1	2
	Infections	2	2	2	2	8	4	3	3	2	5	9
	Miscellaneous	27	32	16	18	54	27	26	29	5	11	21
	No Symptoms	43	52	54	59	123	60	43	49	7	33	61

**) including two pairs of siblings.
*) including one pair of siblings.

Table 4.
Comparison of the Incidence of Abnormalities During Pregnancy in Two Groups of Cases.

	Normal Labour and Normal Neonatal Period				Abnormalities of Labour or/and of Neonatal Period				Total Number of Cases
	No Abnormalities during Pregnancy	Abnormalities during Pregnancy			No Abnormalities during Pregnancy	Abnormalities during Pregnancy			
	Number of Cases	Number of Cases	Per Cent	Total	Number of Cases	Number of Cases	Per Cent	Total	
Hemiplegia, congenital ..	12	11	(48)	23	31	33	(52)	64	87
Paraplegia, congenital ..	24	16	(40)	40	30	21	(41)	51	91
Quadriplegia, congenital ..	26	14	(33)	40	95	68	(42)	163	203
Total	62	41	(40)	103	156	122	(44)	278	381
Postnatally acquired	28	12	(30)	40	6	7	(54)	13	53

symptoms do not appear to occur in any of the groups with striking frequency. In order to illustrate the possible etiological significance of pathological conditions in pregnancy, the incidence of pathological symptoms in pregnancy is compared in two differents groups, *viz.*, cases in which the delivery was complicated and/or in which symptoms were present in the child from birth (including severe icterus), and cases in which the delivery was normal and pathological symptoms were absent at birth (see Table 4).

It will be observed that although pathological changes in pregnancy are the sole abnormality demonstrable in a certain percentage of the cases, symptoms in pregnancy occur with greater frequency in the group complicated delivery with or without symptoms in the child at birth. Presuming that in the majority of cases in which the delivery was complicated and symptoms were present at birth, birth trauma is an etiological factor it should be anticipated that in the remaining group, in which birth traumata are improbable, a greater incidence of pathological changes in pregnancy might be encountered if these possessed any etiological significance. As mentioned previously, the opposite condition is sooner found, for which reason it must be assumed that these data are beset with quite considerable small rôle in the etiology.

In order to illustrate further the possible etiological significance of changes in pregnancy, the percentage incidence of cases in which pathological changes during pregnancy were the only etiological abnormality encountered in the case history, is recorded in Fig. 2. Finally, the percentage incidence of normal pregnancy within the various diagnostic groups is recorded in the same figure.

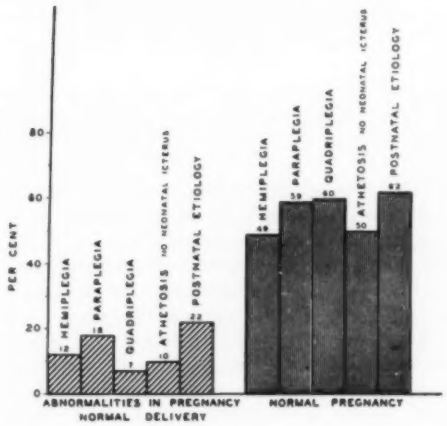

Fig. 2.
A. Percentage Incidence of Cases in Which Abnormalities During Pregnancy Were the Only Known Factors of Possible Etiological Significance.
B. Incidence in Per Cent of Normal Pregnancy.
The Postnatally Acquired Cases are Included for Comparison.

As regards the compiling of information concerning pregnancy and delivery, it should be noted that these data are beset with quite considerable uncertainty, as such information was partly obtained from maternity clinics and physicians and partly by questioning the parents. Whenever possible, extracts from the case histories were obtained. Among others, this was possible in all of the 72 cases which were delivered in the Rigshospital. Questionnaires were sent in all cases in which the child was not delivered at home and more or less adequate answers were obtained in approximately 3/4 of the cases.*)

The possible significance of *anaesthesia*, morphine or morphine derivatives and *oxytocics* could not be estimated from the present material. Morphine was only employed in a very few cases while anaesthesia (most frequently in the form of light obstetric chloroform anaesthesia), on the other hand, was administered to practically all

*) A Danish study of the etiological importance of birth injury in congenital cerebral palsy was published by *Fr. G. Jensen*, Acta Obst. Gyn. Scand., *6:* 392-406, 1927.

the mothers, and pituitrin is employed routinely in Denmark and also in the present material to such a great extent that no conclusions can be drawn.

The *age of the mother* might be expected to play a rôle, partly as regards the course of the delivery and partly as regards the development of the foetus. It appears from Fig. 3 that regarding the age of the mother, the cases are distributed within each group practically as in a normal material. If malformations played an important rôle in the etiology of cerebral palsy, the age distribution of mothers would probably deviate from normal towards the older age groups. As regards quadriplegia only, there appears to be a numerically insignificant preponderance of mothers in the age group 40—45 years.

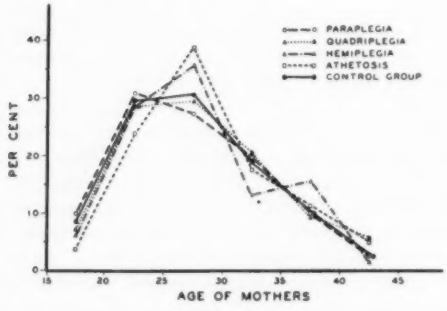

Fig. 3.
Frequency Distribution of Maternal Age Within Each Group. For Comparison is Included the Age Distribution of the Mothers in a Group of 1000 Non-selected Deliveries, S. Nørregaard: Årsagerne til for tidlig fødsel. Arne-Frost Hansens Forlag, Copenhagen 1953.

The distribution of the *birth weights* within the various groups of cerebral palsy appears from Fig. 4 and Fig. 5.

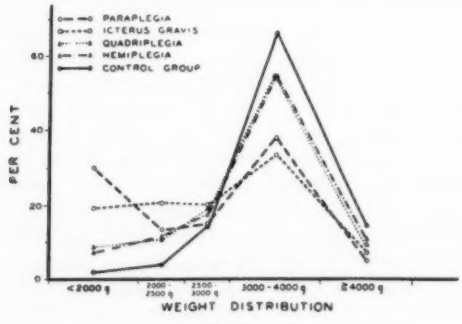

Fig. 4.
Distribution of Birth Weight Within the Various Diagnostic Groups Compared With a Control Group Comprising all Births in Denmark in 1954 (kindly supplied by the Statistical Department of The Danish National Health Board, Head: M. Lindhardt).

It is apparent from Figs. 4 and 5 that birth weights above average are unusual while low birth weight is more frequent in all groups of cerebral

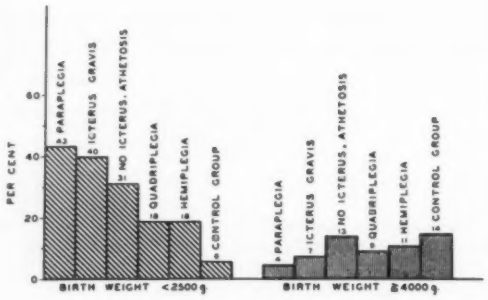

Fig. 5.
Incidence of Birth Weights Below 2500 g and of Birth Weights of 4000 g and more. Control Group the Same as in Fig. 4.

palsy than in a control material. Low birth weight is most common among the cases of paraplegia. The fact that prematurity is observed frequently in "kernicterus" is due to the high incidence of prematurity in the two sub-groups: severe neonatal jaundice without immunization and severe neonatal jaundice without examination of immunization (see also Table 2).

Seasonal Variation. The distribution through the year of live-born in Denmark in 1954 is shown in Fig. 6; it is seen that the seasonal distribution of all weight groups, of prematures and of infants with a birth weight of 4000 g or more is not uniform. In Fig. 7 and Fig. 8 the seasonal distribution of the present series of congenital cases of cerebral palsy is compared with the control group. It will be observed that the cases of paraplegia, in particular, are not uniformly distributed throughout the year. It is possible and perhaps probable that the variations demonstrated are due to the fact that the material is too small, but perhaps the seasonal variation encountered here requires comparison with other materials.

Number in family. The number of first born does not appear to deviate significantly from the normal average (S. Nørregaard, see above). See Fig. 9.

In Fig. 10, in addition, the percentage incidence of first born infants with birth weight of over 3500 g (7 lbs. 12 oz.) is recorded.

The incidence of *complicated delivery* appears from Fig. 11 and the incidence of breech presentation, forceps delivery and Caesarean section is classified under one heading in Fig. 12. Criteria for listing cases in Fig. 11 were: signs of intrauterine asphyxia, meconium in waters, arrest of labour, prolongation of second stage of labour, cord encirclement, placenta praevia, premature separation of placenta, abnormal bleeding, difficulty in delivering head, prolapsed arm, breech presentation, foot presentation, forceps (usually high), and Caesarean section.

Asphyxia neonatorum was encountered with varying frequency in the various groups of cere-

bral palsy, most frequently in cases of athetosis not preceded by severe icterus neonatorum. See Fig. 13.

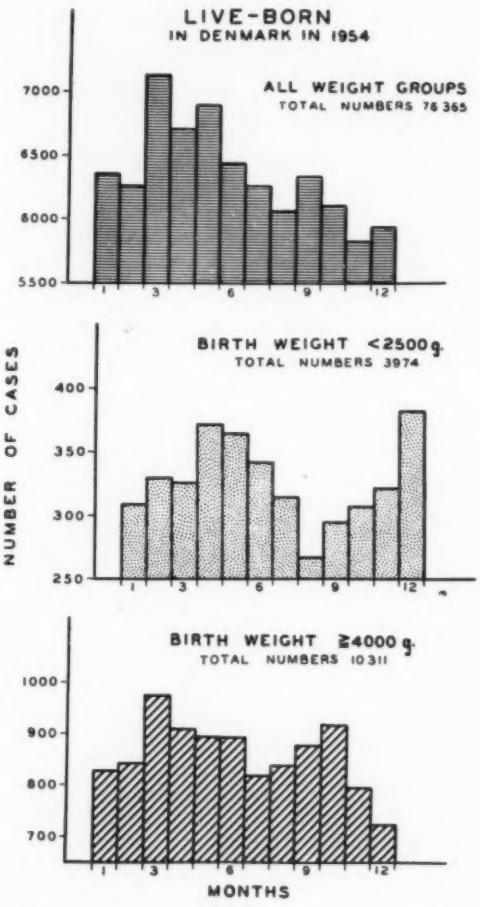

Fig. 6.
Distribution Through the Year of Deliveries of Live-Born in Denmark.

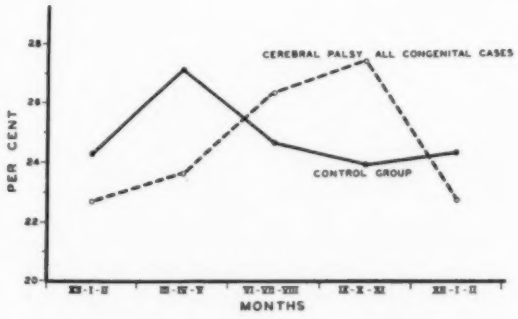

Fig. 7.
The Seasonal Distribution of Time of Birth of the Present Series of Cerebral Palsy Compared With a Control Group. (Same as in Fig. 6).

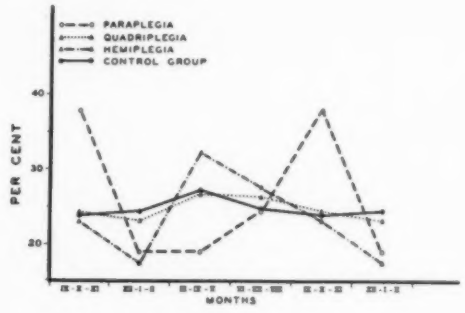

Fig. 8.
The Seasonal Distribution of Time of Birth of the Present Series of Spastic Hemiplegia, Paraplegia and Quadriplegia Compared With a Control Group. (Same as in Fig. 6).

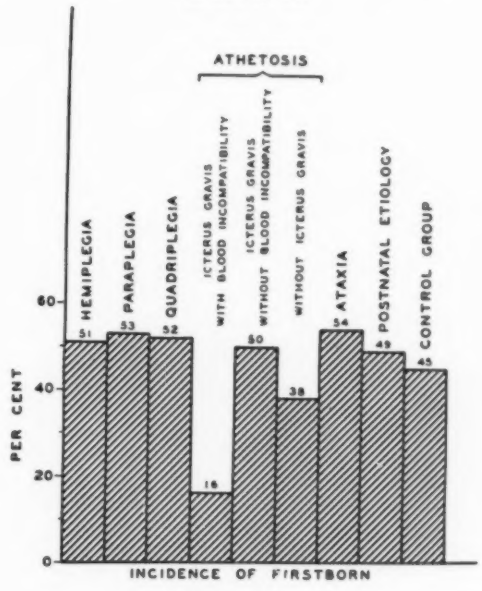

Fig. 9.

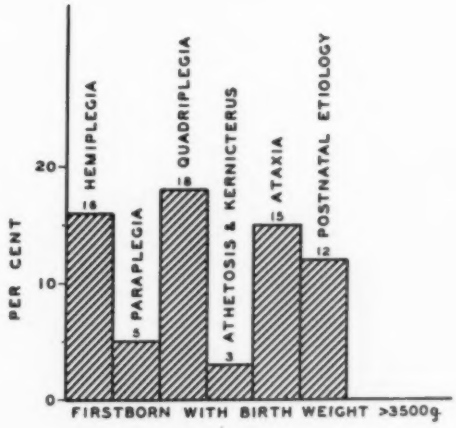

Fig. 10.

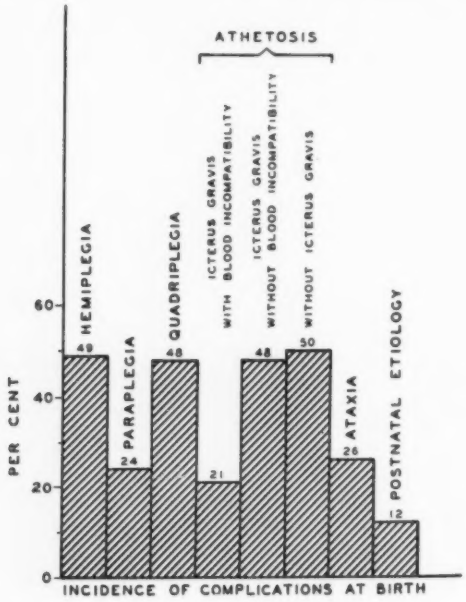

Fig. 11.

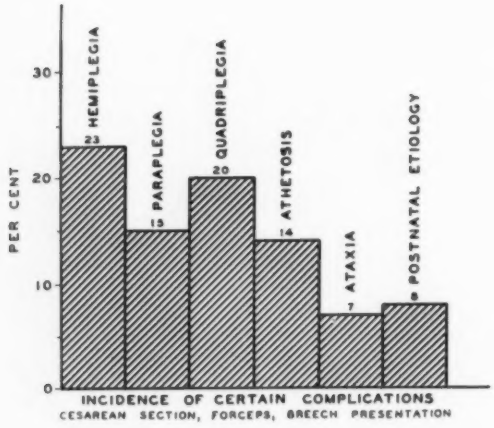

Fig. 12.

Symptoms during the first days of life. Attacks of cyanosis, twitching, seizures, tense fontanelle, opisthotonus, limpness and inability to suck are well known and common symptoms in cerebral palsy, but as it will appear from Fig. 14 they occur with varying frequency within the various groups.

Icterus neonatorum probably only plays a part in the development of cerebral palsy when present to a pronounced degree and for a prolonged period. In the present series, severe and prolonged icterus occurs nearly exclusively in the group of athetosis. The incidence of severe icterus is recorded in Fig. 15.

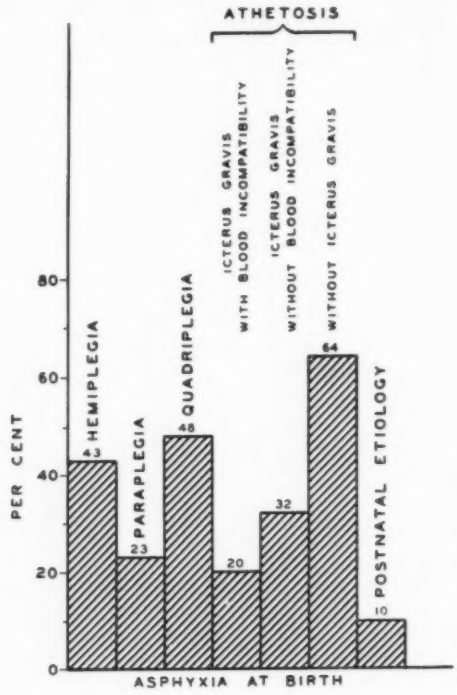

Fig. 13.

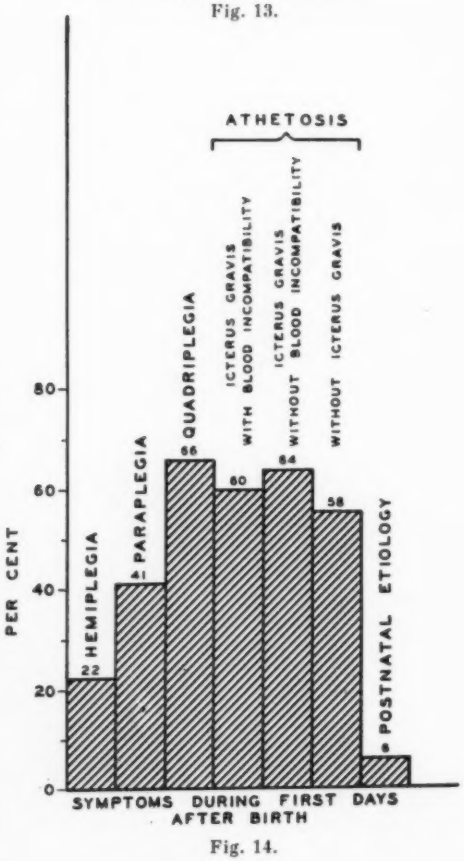

Fig. 14.

Clinical Data.

Of the clinical data in the present material, only a rough account will be given of certain symptoms which are of particular significance in incapacitating the patient, such as mental deficiency, seizures, microcephaly, strabismus and impairment of vision and hearing.

It will be observed from Fig. 16 that *defective intelligence* occurs much more frequently among patients with quadriplegia than in patients with hemiplegia, paraplegia and athetosis.

It should be noted that the estimation of the intelligence is mainly based on a careful case history in connection with personal knowledge of the

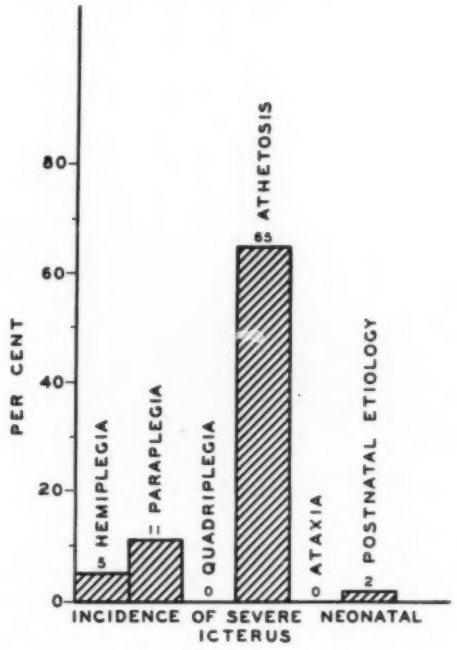

Fig. 15.

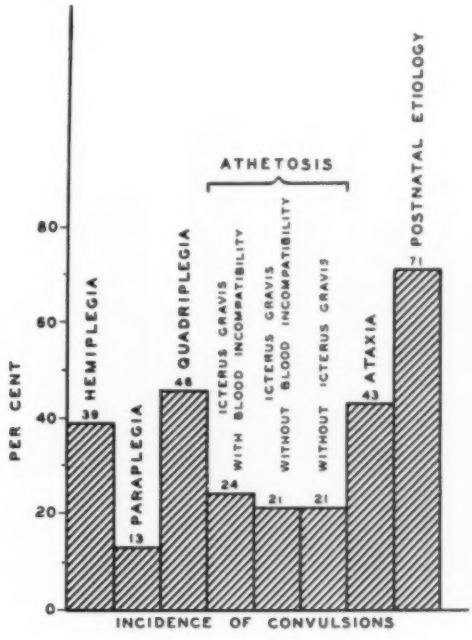

Fig. 17.

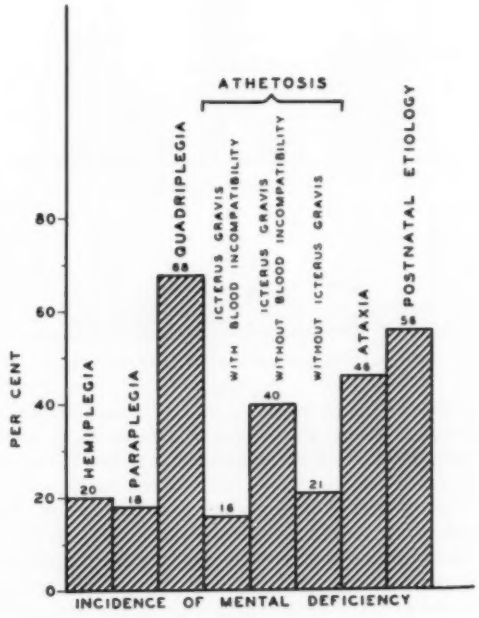

Fig. 16.

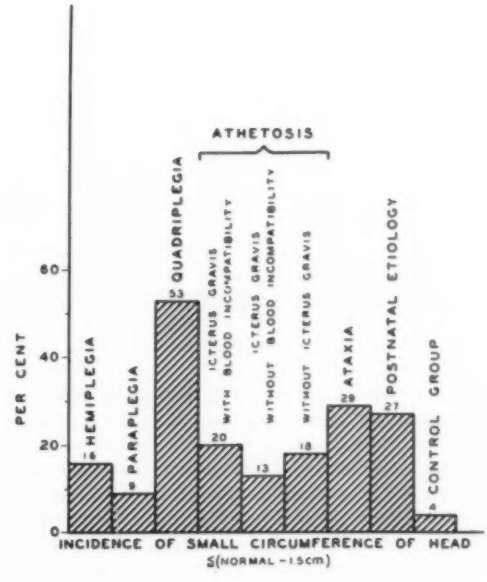

Fig. 18.

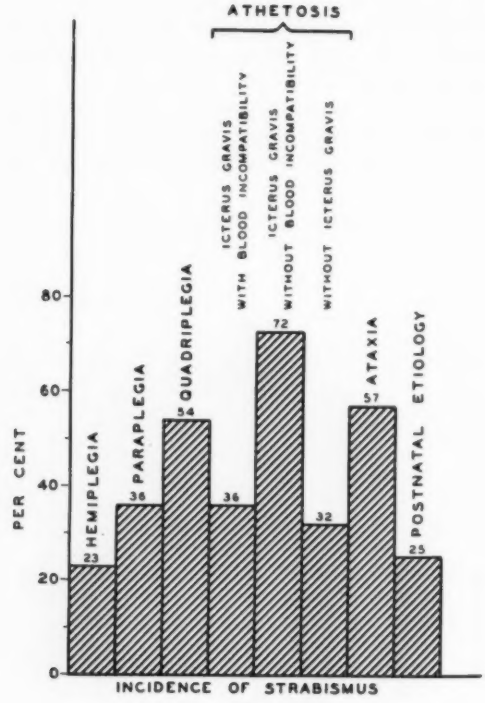

Fig. 19.

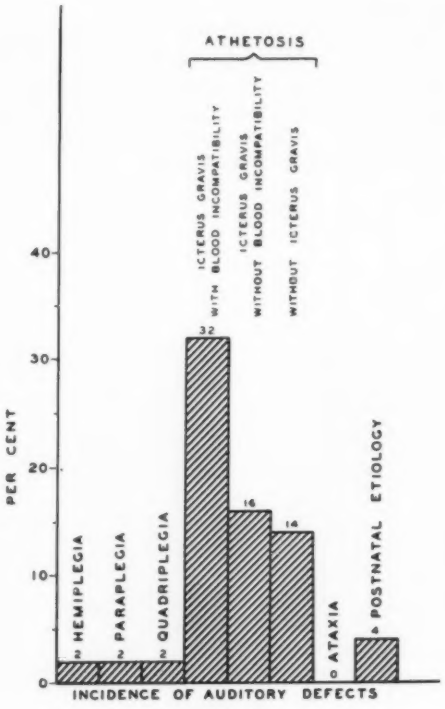

Fig. 21.

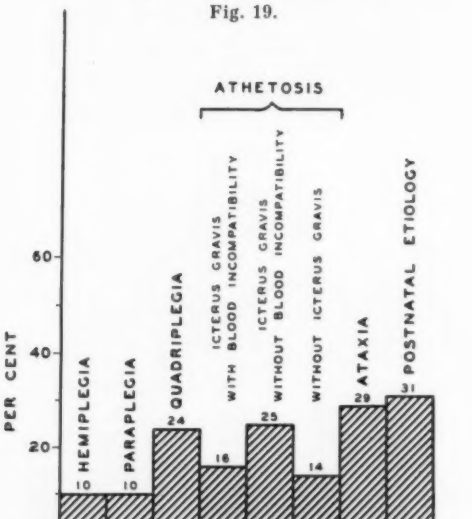

Fig. 20.

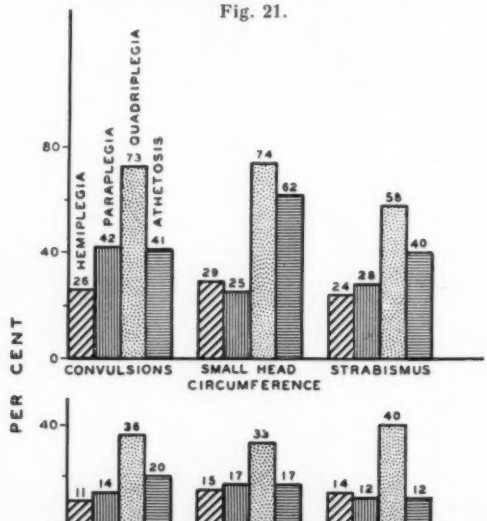

Fig. 22.

Incidence of Mental Deficiency in the Various Diagnostic Groups in the Presence and Absence of Convulsions, Small Head Circumference, and Strabismus.

child throughout a prolonged period, and that intelligence tests were employed only to a limited extent.

Seizures and spasms occurring in attacks were found most frequently in the groups of hemiplegia and quadriplegia, see Fig. 17. In the group of cases with ataxia, seizures were similarly found in a large proportion of the patients, but all the accounts concerning ataxia in the present series are beset with considerable uncertainty on account of the small number of patients.

The head circumference appears from Fig. 18. The term *small head circumference* indicates a circumference which is more than 1½ cm, most frequently 2 cm, less than normal for the age.

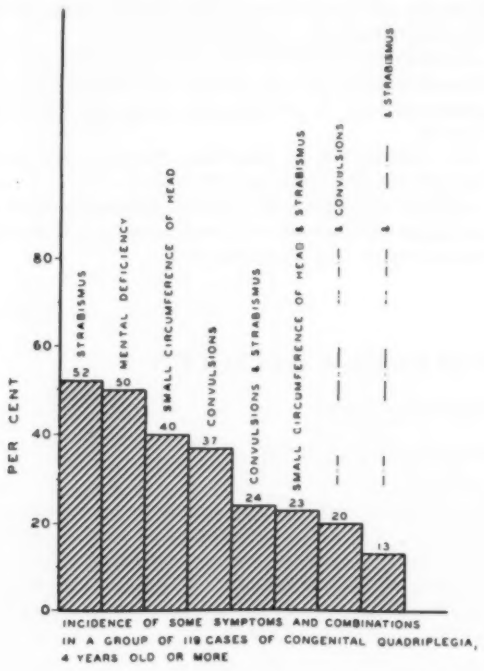

Fig. 23.

The percentage incidence of *strabismus*, of *impairment of vision* and of *impairment of hearing* appears from Fig. 19, 20, and 21.

As regards the cases of hemiplegia, paraplegia, quadriplegia, and athetosis, the relation between the incidence of imbecility and seizures, small head circumference and strabismus is recorded in Fig. 22.

The incidence of the individual symptoms for the group of quadriplegia in patients over the age of 4 years is recorded in Fig. 23 and the relation of these to mental deficiency in Fig. 24.

As is seen, the clinical group of cerebral palsy is not at all homogeneous, not only regarding the motor functions but also with respect to the intelligence. The incidence of mental deficiency within the various diagnostic groups of cerebral palsy differs a great deal, and within the single groups the incidence of mental deficiency is higher in the presence of certain symptoms, *viz.*, convulsions, small head circumference and strabismus.

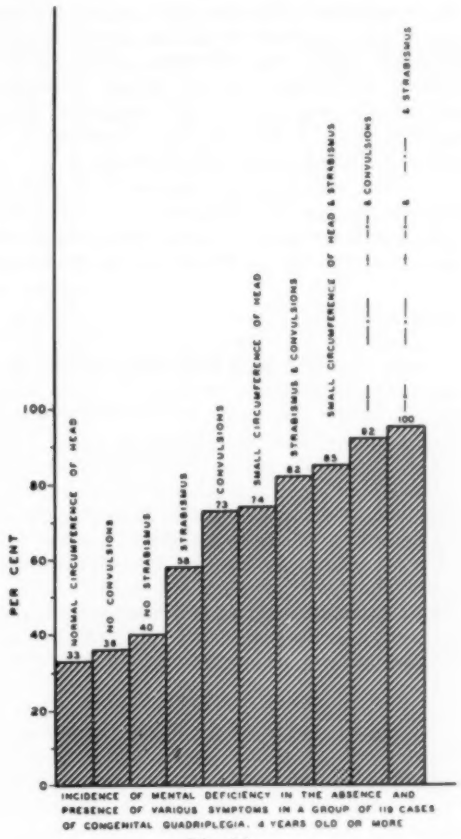

Fig. 24.

Summary.

1. A numerical account and classification of the case histories and clinical data concerning 543 cases of cerebral palsy, examined by the author, are recorded. The attention is drawn to the fact that the group of cases of quadriplegia comprises a larger proportion of the total series than is usual, because particularly the most severely affected patients are admitted to The University Clinic of Paediatrics.

2. Cases with a hereditary disposition appear to play a numerically small part.

3. The number of cases developing post-natally is greatest in the groups of hemiplegia and ataxia.

4. Pathological conditions during pregnancy are, as a whole, scarcely of any great etiological significance in the development of cerebral palsy. Toxaemia of pregnancy and metrorrhagia probably constitute exceptions.

5. The age of the mother does not appear to be of noteworthy significance. In this respect cerebral palsy differs from what is generally found in congenital malformations.

6. Low birth weight occurs more frequently than normal in all the groups of cerebral palsy, most frequently in the group of paraplegia, while a high birth weight does not seem to be of importance.

7. There appears to be a certain seasonal variation in the incidence of cerebral palsy, particularly of paraplegia. The distribution through the year of live-born in Denmark in 1954 was examined. It was found that the seasonal distribution of prematures and of infants with a birth weight of 4000 g or more is different from that of all weight groups. This may to a certain extent explain the seasonal distribution of cerebral palsy.

8. Complicated deliveries occur more frequently than normal, particularly in the groups hemiplegia, quadriplegia and athetosis, while asphyxia is noted particularly in the groups hemiplegia, quadriplegia and ataxia, and symptoms during the first days of life are most frequent in the groups of quadriplegia and athetosis.

9. Severe and prolonged icterus is greatly predominant in cases of athetosis.

10. Mental deficiency is encountered more than twice as frequently in the group of quadriplegia as in the three groups of hemiplegia, paraplegia and athetosis.

11. Seizures and fits occur approximately twice as frequently in the two groups of hemiplegia and quadriplegia as in the groups of paraplegia and athetosis.

12. Impairment of hearing occurs nearly exclusively in the group of athetosis.

13. The incidence of mental deficiency is increased in the presence of convulsions, small head circumference and strabismus.

HAEMORRHAGIC DIATHESIS IN CHILDREN

A FOLLOW-UP EXAMINATION

By THORKILD FRIIS & PEER PÆRREGAARD

The object of this work is to study the tendency to relapse in children previously admitted to hospital with symptoms of haemorrhagic diathesis. The material does not include cases of aplastic anaemia, leukosis and haemophilia, which have a serious prognosis determined by the basic diseases.

PREVIOUS INVESTIGATIONS

Clement & Diamond (1) examined 140 children with haemorrhagic diathesis, 96 of whom had thrombopenia. The observation period was 2 years. The cases without thrombopenia recovered spontaneously, with the exception of two, in which symptoms persisted. The prognosis for the thrombopenic cases was poorer, since four died of this disease before the follow-up, while 19 had symptoms of haemorrhagic diathesis.

In Diamond's material (2), the prognosis was also dubious. His material included 28 children with haemorrhagic diathesis with thrombopenia. The spleen was removed in 8 of these cases, 2 of which died and the remainder recovered. Of the remaining 20, 2 died of intracranial bleeding, while 6 still had symptoms of haemorrhagic diathesis 10 years later. Twelve had recovered completely.

Elliott (3) states that the prognosis in thrombopenia is considerably better in children than in adults.

Linneweh (5) is of the opinion that on this account hesitation should be shown in recommending splenectomy in children with thrombopenia.

Heinild & Lindgren (4) followed up 113 cases of thrombopenia in children. The prognosis in the essential form was found to be excellent, since only one child out of 41 died in the course of 9.4 years. However, the prognosis was poorer in cases of thrombopenia caused by infections (13 fatal cases out of 63), or as a link in systemic disease (7 died out of 9).

McLean, Kreidel & Coffey's (6) study comprises 21 cases of thrombopenia in children. It is indicated that no definite relation could be found between reduction in the number of thrombocytes and the tendency to bleeding. Fifteen patients were treated conservatively. One of these died. The spleen was removed in 6 cases and 3 of these children died.

Newton & Zuelzer (7) examined 47 cases of thrombopenia in children. The majority of the patients were boys. In 53 per cent the bleeding was caused by infections, particularly of the upper respiratory tract. In one instance only were there similar cases among the nearest relatives. Capillary resistance, determined by means of the Bexelius test, was reduced in only 23 of the 32 cases examined. Forty of these patients were treated conservatively. Of these 2 died and 3 suffered relapse in the course of six months.

The general conclusion to be drawn from the above-mentioned studies, with the exception of two (1, 2), is that the prognosis in haemorrhagic diathesis with thrombopenia is good in children. Haemorrhagic diathesis without thrombopenia has been mentioned in one report only (1), and here the prognosis was found to be excellent.

MATERIAL

Out of a total of 85 patients with haemorrhagic diathesis admitted to hospital during the period 1944—1953, 64 (75 per cent) were followed up. (All patients were called in twice by correspondence). A higher follow-up percentage would have been desirable, but many of the patients living outside Copenhagen did not respond to the re-

From: Martinsvej Children's Hospital (Chief: *E. Winge Flensborg*), Blegdamshospitalet (Chief: Prof. *H. C. A. Lassen*) and The Paediatric Department of the University Hospital, Rigshospitalet (Chief. Prof. *P. Plum*).

quest to attend. Twenty-six of these cases were from the Martinsvej Children's Hospital, 23 from the Blegdamshospital, and 15 from the Paediatric Department of the University Hospital. The observation period was from 1 to 9 years (average 4.1 years).

Age at time of admission will be seen from Fig. 1, which shows that the tendency to bleeding was greatest in the ages 1—8 years. This confirms Clement's (1) and Newton's (9) findings.

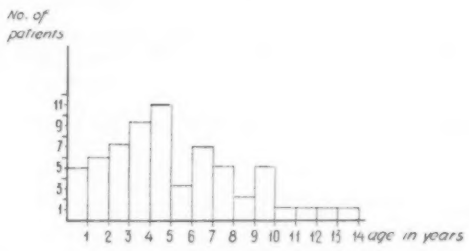

Fig. 1.

In three instances only were there similar cases among near relatives. Of these three, one was caused by pneumonia, and in the other two cases the cause was unknown one of the three thrombopenic and the others non-thrombopenic.

Bleeding was somewhat more frequent in boys than in girls (37 boys and 27 girls), as found also by Newton (7) and others.

The patients followed up have been divided according to aetiology, as shown in Table 1.

Table 1.
Aetiology of bleeding on admission to hospital.

	Thrombopenia	No thrombopenie	Thrombocytes not examined	Total
Bleeding occurred in connection with infection ..	8	22	1	31
Bleeding occurred on an allergic-toxic basis	2	4	0	6
Bleeding occurred for unknown reasons	14	11	2	27
Total	24	37	3	64

The majority of the cases were caused by infections (Group 1), 18 of these being due to infections of the upper respiratory tract, 5 to contagious children's diseases, and 8 to infections of other types. Non-thrombopenic cases predominated. The infection was present either at the time of bleeding or had disappeared later than 14 days before commencement of bleeding.

Group 2 includes the cases where bleeding seems to have been caused by some known substance, or where the clinical condition was allergically characteristic. The causes are assumed to be: Neoalfasol, Lucosil, whooping-cough vaccine, and sodium arsenite. No cause could be found in two cases, but in addition to skin bleeding, one of these patients had a universal outbreak of urticaria with eosinophilia, and the other Besnier's prurigo with asthma.

Among the cases of unknown aetiology (Group 3), those with thrombopenia were just as frequent as those without thrombopenia, as opposed to the other groups.

It will also be seen from the table that there were 24 cases with thrombopenia. Of these, 17 had prolonged bleeding time (longer than 6 minutes) and 13 showed positive reactions to the capillary resistance test (more than 10 petechiae). Of the 40 patients without thrombopenia, only 6 had prolonged bleeding time and 7 positive capillarly resistance test.

Before the result of the follow-up is reported, brief mention will be made of the site of bleeding at time of admission to hospital (Table 2).

Table 2.
Site of bleeding on admission to hospital.

	Thrombopenia	No thrombopenia	Thrombocytes not examined	Total
Skin bleeding	24	34	3	61
Joint bleeding	4	11	0	15
Bleeding from nose, ear, and mouth cavity	7	6	1	14
Bleeding from intestines	2	9	0	11
Haematuria	3	1	0	4

It will be seen that all the patients except three had skin bleeding. Of the three exceptions, one had haemarthrosis (prolonged bleeding time) and two haematemesis (positive capillary resistance test). It will also be seen that all the thrombopenic cases had skin bleeding, and that the patients with joint and intestinal bleeding did not have thrombopenia so often.

In no case could lymph node or spleen swelling be demonstrated.

Examination of bone marrow was carried out in six cases only. Four of these showed no abnormality, except for a displacement to the left in the erythropoiesis. An increased number of megacaryocytes was found in one case (thrombopenia of unknown cause), and pronounced eosinophilia was seen in one case (allergic disease with urticaria).

RESULTS OF FOLLOW-UP STUDY

As mentioned above, the average observation time was 4.1 years. Follow-up examination included determination of bleeding and coagulation

Pathological findings at follow-up examination. At time of hospitalization.

Aetiology	Sex	Age in years	Clinical findings	Thrombocytes	Bleeding time	Coagulation time	Bexelius	Prothrombin time
Unknown	M	1	Skin bleeding. Blood in faeces.	16,000	>15	6	40	39 (24)
Unknown	M	3	Skin bleeding. Haematuria.	4,200	12	6	3	24 (18)
Unknown	F	5	Skin bleeding. Joint swelling.	45,000	4½	7	+	27 (24)
Simultaneous tonsillitis	M	4	Skin bleeding.	41,000	13	10	25	27 (23)
Simultaneous continued fever	M	5	Skin bleeding. Blood in faeces. Oedema.	225,000	5	5	8	—
Sodium arsenite poisoning	F	2	Skin bleeding.	11,000	2½	—	0	—

times, platelet counts, prothrombin time determination, and capillary resistance test.

The bleeding time was measured by pricking in the ear and absorbing the blood on filter paper every 30 seconds until the bleeding ceased. If this occurred within six minutes, the test was considered normal.

The coagulation time was determined by drawing ear blood into a capillary tube, and then breaking off small pieces of the tube until marked coagulation could be seen. If coagulation occurred within eight minutes, the test was considered normal.

The prothrombin time was determined by Quick's method, as modified by Plum, Dam & Hjalmar Larsen.

Capillary resistance was determined a. m. Bexelius with a blood pressure armband placed on the upper arm and inflated to a pressure of 80 mm Hg for three minutes. The number of petechiae in the plica cubiti in a circle of 4 cm diameter must not exceed 10 in a normal reaction.

Thrombocyte counting took the form of microdetermination (as described by Plum), using ear blood mixed with equal parts of 3 per cent citrate solution in a wide pipette. After being allowed to stand for one hour, the blood plates were counted in 16 small squares in the Thomas counting chamber (height of chamber, 0.05 mm), and the result multiplied by 1000. Values over 100,000 are considered as normal.

Out of the 64 patients, 3 had died before the follow-up. Two died during the initial hospitalisation. One of these, a girl af 7 years of age with severe skin bleeding of unknown aetiology, died of cerebral haemorrhage before the state of the thrombocytes had been examined. The other, a girl of 12 years of age with thrombopenia of unknown cause, died during profuse bleeding from skin and mucous membranes. Splenectomy had been carried out two weeks previously, without causing any improvement in the condition. The third of the patients who died, a boy of 2 years of age, who was admitted with non-thrombopenic skin bleeding in connection with acute gastroenteritis, died two years later from unknown causes. Post-mortem revealed status thymicolymphaticus.

Follow-up of the remaining 61 patients gave the following results:—

Two showed manifest bleeding. One was a boy who had skin bleeding, thrombopenia, prolonged bleeding time, and positive capillary resistance test. The other, also a boy, had haematuria and thrombopenia. Both had thrombopenia during the original bleeding, the aetiology of which was unknown.

Four showed abnormal laboratory findings, but no manifest bleeding. In two cases thrombopenia only was found, in one thrombopenia and positive capillary resistance test, and in one positive capillary resistance test only. The aetiology of the original bleeding was in one case unknown, in two cases infection, and in one presumed ingestion of chemicals (sodium arsenite). All patients, except one, had thrombopenia during the original bleeding (see also Table 3).

Four patients had anamnestic data pointing to relapse but showed no objective sign of this at the follow-up, at which time the blood examination was also normal. Two had tendency to spontaneous skin bleeding, one had bleeding tendency in connection with colds, and one in connection with slight injury.

At follow-up.

Anamnestic findings	Clinical findings	Thrombocytes	Bleeding time	Coagulation time	Bexelius	Prothrombin time	Observation period years
Spontaneous skin bleeding	Skin bleeding	38,000	10	—	+	30 (29)	1½
None	Haematuria	60,000	3	4	0	—	6
Spontaneous skin bleeding	None	63,000	3	3	11	—	4
Skin bleeding connected with colds	None	92,000	1½	2½	0	—	4
None	None	35,000	2½	3	20	—	2
None	None	280,000	2	1	13	20 (18)	7

DISCUSSION

The prognosis for haemorrhagic diathesis in children is relatively good, when this condition does not occur as an accompanying phenomenon in cases of aplastic anaemia, haemophilia, and leukosis. At a follow-up examination of 61 cases (out of a total of 85 patients previously admitted to hospital), with an average observation period of 4.1 years, only 6 (9.8 per cent) showed signs of tendency to bleeding (by clinical or laboratory findings). Three patients had died before the follow-up, two on account of bleeding (4.7 per cent).

These findings are in general agreement with previous investigations, which, however, comprise chiefly cases of thrombopenia (3, 4, 5, 6, 7). Clement et al. (1) mention that the prognosis is better for patients without thrombopenia than for those with that disease. The present study also shows that 5 of the 6 patients who had symptoms of haemorrhagic diathesis at follow-up had thrombopenia originally.

On the basis of this material, the advisability of carrying out splenectomy in cases of thrombopenia would appear to be doubtful, because of the good prognosis with conservative treatment. In the one case where splenectomy was performed, the patient died. Demonstrable spleen swelling was not found in any of the cases, and this is in agreement with the experience of Clement et al. (1).

The lack of relationship between possible reduction in the number of thrombocytes and the tendency to bleeding is in agreement with the findings of McLean et al. (6), and the finding that capillary resistance determined by the tourniquet test is reduced in relatively few cases, is the same as that arrived at by Newton et al. (7). It is quite obvious that only very few of the non-thrombopenic cases had prolonged bleeding time and positive tourniquet test.

Similar cases among the nearest relatives were found in three instances only. This is also in agreement with the results of Newton et al. (7).

SUMMARY

Follow-up examination has been carried out in 64 children with haemorrhagic diathesis (patients with aplastic anaemia, leukosis and haemophilia have not been examined). The average observation time was 4.1 years (1—9 years).

Three patients had died before the follow-up (two from bleeding) and six showed signs of haemorrhagic diathesis at the later examination.

Thus, the prognosis for haemorrhagic diathesis is relatively good in children, though it appears to be somewhat better in the non-thrombopenic cases than in those with thrombopenia.

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DIPHTHERIA IN DENMARK

FROM 23,695 TO 1 CASE — POST OR PROPTER?

By TH. MADSEN and STEN MADSEN

I. SERUM THERAPY

By TH. MADSEN

In the latter decades of the nineteenth century, diphtheria was the most dreaded of all children's diseases. The disease was feared as much as poliomyelitis today but by far surpassed it both as regards incidence and mortality.

Following a few minor epidemics in 1845—50 and 1863—67, the number of notified cases of diphtheria (Figure 1) rose to a maximum of 23,695 cases in 1893 and a lethality (case fatality) of 10—12 per cent. Adapted to the present population of Denmark, this figure corresponds to approximately 50,000 cases per annum with 5,000—6,000 deaths, equalling the number of deaths from all the other infectious diseases of childhood taken together. It will be understood that in those days "a visitation from the Angel of Death throughout the country" was a current phrase.

A difficulty exists in the comparison of the figures from different periods: at that time bacterial differential diagnosis of diphtheria was not available. This did not become general until the end of the nineties following the work of P r i p and F i b i g e r. By the bacteriological investigation, a number of non-diphtheritic anginas could be excluded, while, on the other hand, many quite mild cases were included. The fact that a number of physicians even recorded symptom-free carriers did not facilitate comparison between early and later official medical accounts either. Comparison of the lethality from different countries also suffers from the difficulty that the figure for lethality depends on the method of notification, particularly on the number of mild cases recorded.

While the discovery of diphtheria antitoxin by B e h r i n g in 1890 did not awake much therapeutic interest outside Germany, a tremendous sensation was caused all over the world when R o u x, at the Congress of Hygiene in Budapest in September, 1894, recorded his results obtained in "Hôpital des Enfants Malades" by treatment with a diphtheria serum prepared in the Pasteur Institute. From February until July 1894, 448 children were treated, the lethality being 24.5 per cent compared with the average lethality from the preceding years of 51.7 per cent. During the same period, approximately 60 per cent of the children died in "Hôpital Trousseau" where serum was not available.

Great efforts were made throughout the world to produce diphtheria antiserum and in Denmark C. J. S a l o m o n s e n, then Reader in Bacteriology, obtained for this purpose a grant of approximately £ 500 for the University Laboratory of Medical Bacteriology in Copenhagen.

This serotherapeutic department was started under very primitive conditions; the laboratory consisted of a couple of entrance rooms in the front house in 11, Ny Vestergade, and the experimental animals were housed in an old stable in the yard, while some horses were stabled in the High School for Agriculture (1).

After various difficulties, particularly in the preparation of diphtheria toxin (2), the Danish serum became available in the summer of 1895. Already in the autumn of 1894, Professor S. T.

Read at the Danish Medical-Historical Society, March 12th, 1956.

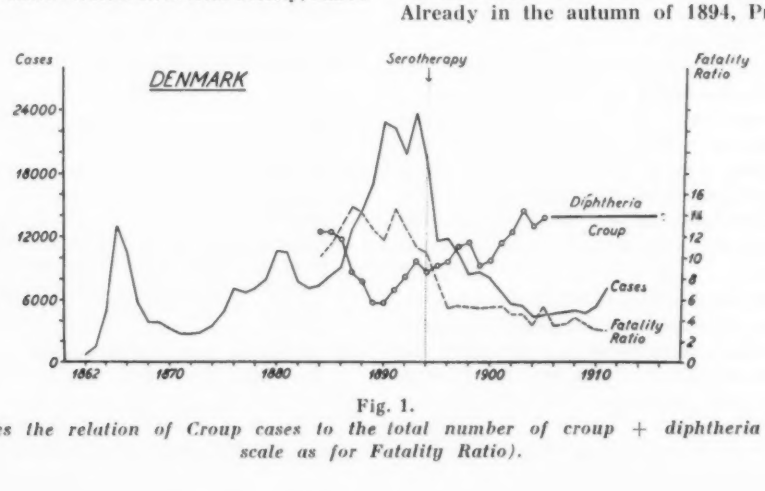

Fig. 1.
o-o-o indicates the relation of Croup cases to the total number of croup + diphtheria cases (same scale as for Fatality Ratio).

Sørensen at Blegdamshospitalet (Hospital for Infectious Diseases, Copenhagen) attempted serum therapy with the small quantities of German serum at his disposal, but his initial experiments did not provide any criteria for favourable results from this new preparation (3). He stressed the difficulties in the evaluation; an important factor amongst these was that diphtheria had assumed an unusually benign character in the year 1895, so that months might elapse without a single death. He further elaborated this point during his experiments with French and Danish sera from April, 1895. He attempted, as far as possible, to compare the cases treated with serum with a control series and still came to the result that serum therapy neither modified the course of the disease nor reduced the lethality (4). He stressed, however, that in his opinion secondary invasion of the respiratory tract (croup) was definitely rarer in the cases treated with serum. Although obviously doubtful about serum therapy, he took entirely objective view point and maintained that his figures were small and the control experiments difficult.

From neighbouring Scandinavian countries, quite conflicting reports regarding the value of the serum were published.

Thure Hellström (5, 6), Stockholm, was rather sceptical and pointed out that both in extent and severity diphtheria had been receding markedly prior to the introduction of serum therapy. He stated that the lethality from diphtheria in Stockholm fell very markedly in the course of 1894, *viz*, without serum:

1894.

	Of All Notified Cases	Of Children Under the Age of 10 Years
1st. Quarter	32.8 %	38.3 %
2nd. "	23.6 %	34.7 %
3rd. "	14.2 %	20.3 %
4th. "	5.8 %	9.0 %

On the other hand, Aaser in Oslo (7) became immediately very optimistic and maintained a lifelong enthusiasm.

In Norway, the lethality for the entire country remained more or less unchanged from 22 per cent to 25 per cent during the years 1890—1894 and thereafter fell abruptly to approximately 13 per cent in 1895. It is tempting to attribute this abrupt fall to serum therapy which was initiated in 1895 although it was only employed to a limited extent outside Oslo. But when the state of affairs in Oslo proper is considered, Figure 2 shows that already from 1892 a great fall in the lethality is noticeable, so that serum therapy was initiated during a very steep fall in the mortality.

It is odd that a man of such experience as Yngvar Ustvedt in the Textbook of Medicine in 1927 ("Lärebog i Intern Medicin"), mentioning the prognosis in diphtheria, reproduces the curve from Oslo and stresses that "the introduction of antidiphteritic serum constitutes the decisive change".

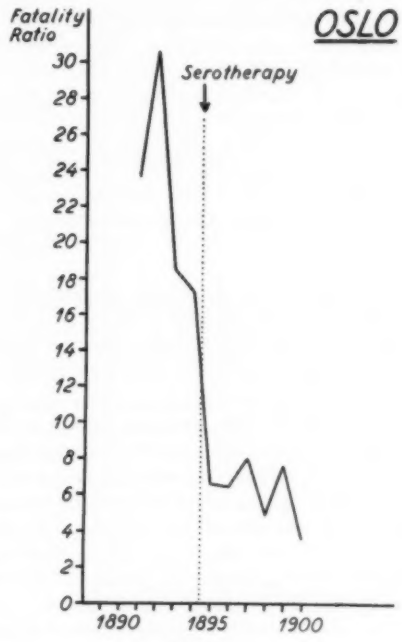

Fig. 2.

As Danish serum gradually became available in 1895, serum therapy became more and more extensive in Denmark. The impression of its effect was by and large favourable.

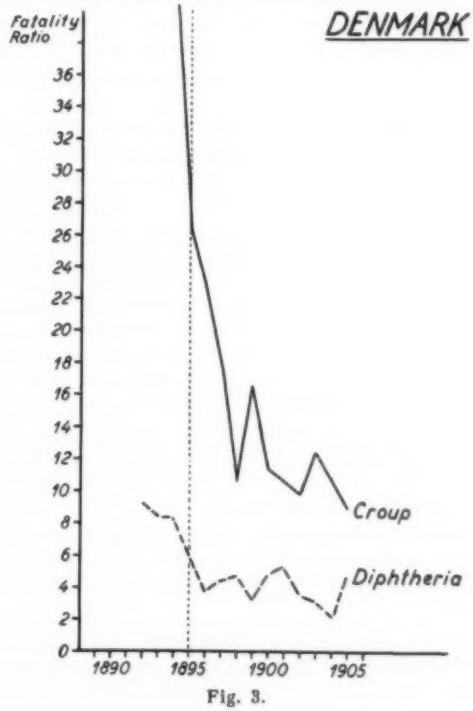

Fig. 3.

As an example, accounts from two neighbouring hospitals in Jutland, Viborg and Skive, are recorded; there the lethality rates from diphtheria were:

	Viborg %	Skive %	
1892	16.4		No Serum Therapy
1893	14.3	6.36	"
1894	11.3	7.01	"
1895	7.3	3.52	Partial Serum Therapy
1896	0.97	2.56	Serum Therapy Exclusively

It was essential to be aware of the fact that the lethality was decreasing already prior to the introduction of the new therapy in order to avoid incorrect evaluation of the effect of serum.

It is easy to understand that many physicians were influenced by the fact that they saw fewer cases, fewer deaths and milder diphtheria. For them the possibility of sober judgment was extremely difficult as the new therapy was introduced in the middle of the abrupt fall in the incidence of cases following the great wave of diphtheria which occurred in many European countries in the middle of the nineties.

This is particularly striking when the lethalities for croup and diphtheria are considered individually (Fig. 3). The favourable effect of serum therapy on croup particularly impressed the contemporary physicians, but this fall in lethality had already begun in 1893.

During the great epidemic wave in 1887—1895, the relative proportion of croup to diphtheria was diminishing, but during the years after 1895 when the figure was approximately 9, it rose to approximately 14 in 1903, although serum therapy had been employed to the full extent during these years (Fig. 1).

For these years, notification must be regarded as fairly reliable, as bacteriological diagnosis of diphtheria was employed to a great extent, while previously no definite criteria in the differentiation between diphtheritic croup and croup of catarrhal origin had been available. The peculiar phenomenon that the incidence of croup rose while the incidence of diphtheria fell has already been stressed by A. Johannesen (8) in Norway and by J. Carlsen (9) in Denmark, amongst others. These authors maintain that the incidence of diphtheria is in inverse proportion to the tendency to attack the larynx, *viz.*, the more infrequently diphtheria occurs, the more frequently is the croupous form encountered among the total number of cases.

There is suggestion that a similar state of affairs is encountered in the last epidemic wave in the forties but the figures are admittedly very small.

Serum therapy was continuously the object of criticism and in Danish official medical accounts from 1895 and the subsequent years, several annotations are found stating that diphtheria had become much milder and that many cases recovered even without serum therapy.

During this period of uncertainty as regards the favourable effect of serum therapy, Fibiger recommended Sørensen to treat all patients admitted one day with serum but none of those admitted on the following day. This experiment extended from May 13, 1896 to May 13, 1897.

The senior author of the present paper was himself house physician at the Blegdamshospital in the spring of 1897 and naturally hoped to see favourable results from the serum he had helped to prepare but, quite honestly, could find no striking difference between the two groups of patients. In these spring months, diphtheria had become markedly milder, even in the non-treated cases. The following discrepancy between the two experimental groups did not become apparent until the final calculation (10):

Diphtheria			†	Lethality	Croup			†	Lethality
204	+	Serum	5	2%	35	+	Serum	3	8%
201	0	Serum	15	7%	43	0	Serum	15	35%

These figures, a number of which were quoted by Fibiger in connection with Th. Madsen's thesis (2) in December 1896, appeared very convincing, not least because a recognized medical statistician had supported them. They strengthened to a great extent the clinicians' belief in the effect of serum and contributed much to counteract the criticism which recurred regularly. It became regarded as nearly hyppocrisy not to believe in the value of serum. From various parts of Europe, disappointment was expressed that at the end of the epidemic wave of diphtheria towards the turn of the century, the same dramatic effect of serum therapy which presumably occurred during the abrupt fall in 1894—96 could no longer be observed.

Thus Roux, about the year 1900, heard from his French colleagues the remark: "Votre serum ne fait plus tomber les membranes" which stimulated him to attempt to prepare an antibacterial serum. This, however, did not produce any striking result either.

In Denmark, also, the great enthusiasm expressed about the good results thought to have been achieved during the first period of the therapy was replaced by more sober consideration. Slight disappointment prevailed that the lethality could not be reduced further than to 3—4 per cent. Following the animal experiments and the good results obtained with passive immunization, the conclusion was justified that early injection of diphtheria antitoxin might prevent newly formed toxin from combining with the cells, but is was apparently very difficult to cure a body in which the toxin was already fixed in the organs and had injured them.

In 1902, The Serum Therapeutic Department was replaced by The State Serum Institute (Sta-

tens Seruminstitut) and great effort was made to achieve better results. Attempts were made to obtain a rational basis for serum therapy by investigation of the resorption and excretion of antitoxic serum following various methods of administration. This led to the recommendation of administering a large dose of serum, possibly the total amount required, as early as possible and intravenously (11, 12).

A more potent serum was prepared by selecting particularly good antitoxin producers from among the serum horses while, among others, S. Schmidt and his co-workers freed the serum from inactive and toxic constituents and simultaneously concentrated it. Finally, in co-operation with S. Schmidt, the avidity of the diphtheria antitoxin was studied so that a particularly effective serum could be put at the disposal of the clinicians (13).

Professor Bie (14) at the Blegdamshospital was extremely cooperative in all these endeavours. He employed larger doses intravenously of the potent serum and was himself of the opinion that a reduction in the lethality had thereby been obtained. As a suitable control material is not available, it is very difficult to know how much was achieved in this direction. Many experienced clinicians including Peter Holst (15) and H. C. A. Lassen (16), do not regard the very large doses of antitoxin as being of any value.

The question often arose as to why it was impossible to reproduce the striking results which were achieved in the first epoch of serum therapy with small doses of weak serum administered subcutaneously, frequently on the second or third day of the illness or later. The reason is probably that serum therapy was inaugurated at a time which could not have been more unfortunate for sober evaluation, *viz.*, in the middle of a period with markedly declining morbidity and lethality.

The most important and most frequently recorded evidence, namely Fibiger's figures, was also recently subjected to statistical criticism by G. Rasch (17) who demonstrated that on closer analysis they cannot be used as proof of the effect of serum.

This, naturally, does not imply that serum therapy is ineffective. Animal experiments and the good results obtained by passive immunization show the significance of producing an excess of antitoxin in the blood as rapidly as possibly. Doubt exists as regards the necessary amount of antitoxin. It can, however, be estimated that the greatest quantity of diphtheria toxin present in the entire blood volume of a patient seriously infected with diphtheria is only approximately ten times the fatal dose for a guineapig, and this should be neutralized by administration of a few thousand antitoxic units intravenously. By administration of a larger dose of antitoxin the necessary concentration in the blood may be maintained for a sufficient number of days (11, 12).

The fact that patients still come late for treatment presents a difficulty. Cases are, however, still reported which from the commencement are so fulminating, and in which intoxication is present prior to the appearance of the local symptoms, that they cannot be saved even if the most energetic serum therapy be instituted immediately.

As the extent of the membranes in some of these cases is strikingly small, a rapidly developing septicaemia is possibly present. H. C. A. Lassen, among others, has demonstrated diphtheria bacilli in the organs in several cases.

Thus, we have had to revise our previous concept of what may be achieved by serum therapy in diphtheria and recognize that the dramatic results, presumed to be observed in 1895 and the subsequent years, were mainly due to spontaneous changes in the character of the diphtheria. Serum therapy, naturally, although with lesser expectations as regards the therapeutic results, maintains its great significance in the treatment of diphtheria.

At present diphtheria has practically vanished from Denmark and, it is to be hoped, will not return because of the thorough diphtheria immunization. Thus, the original cause of the establishment of The State Serum Institute (Statens Seruminstitut) 54 years ago, *viz.*, the preparation of diphtheria antiserum, has lost its previous significance; it is to be hoped, forever.

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II. DIPHTHERIA IMMUNIZATION

By STEN MADSEN

Diphtheria was defeated by immunization and not by serum therapy.

In the State Serum Institute, Copenhagen, interest has been shown in this immunization ever since the first communication on diphtheria anatoxin by Ramon (1) in 1923. S. Schmidt (2), early, undertook the preparation, and also laeter together with his co-workers A. Hansen, Inga Scheibel et alia (3). They improved the vaccine by adding aluminum hydroxide and proposed various methods of purification. Thereafter immunization of humans, particularly children, was cautiously begun (4), and in 1928 a Public Clinic for Immunization was started in the Serum Institute. There, in the course of the years, over 40,000 children have been immunized free of charge.

A long period elapsed, however, before prophylactic immunization for diphtheria was employed to any great extent. This was mainly due to two circumstances: the first being that in the twenties and the beginning of the thirties, diphtheria had become milder and both morbidity and lethality (approximately 3 per cent) were diminishing (see Fig. 1); the other reason was the great caution shown by leading paediatricians (5) and with them also by the Danish authorities. For example great persuasion was necessary to get the school authorities to permit immunization in the schools. Among those who, during these tempestuous years actively supported the method were Bojlén, Juel Henningsen, Claus Jensen and Ahrend Larsen (6) and great interest was also shown by a section of the press. Immunization received considerable support from the physician-in-charge at the Blegdamshospital, Copenhagen, Valdemar Bie, who undertook the immunization of pupil nurses from 1929 onwards and contributed much towards producing a more favourable attitude among the authorities and physicians.

During the following years, the tempo of prophylactic immunization for diphtheria increased, particularly in Copenhagen where gradually the majority of children in nursery schools and a very large proportion of school children were immunized. The results appeared to be so favourable that in 1941 the City Authorities of Copenhagen decided to introduce prophylactic immunization against diphtheria for all children between 1 and 15 years free of charge. By 1943 this included the entire country as, on the initiative of the Department of Health, a law was passed according to which all young people under the age of 18 years may be immunized against diphtheria free of charge, while all inhabitants within a certain area must be immunized if the disease be declared the object of public treatment within this area.

The result has been highly satisfactory, and gradually the percentage immunized among children of school age in Copenhagen has increased to 90—100, while the remainder of the country has followed suit (Bojlén (8)). One excellent feature is that diphtheria immunization is combined with tetanus immunization and that the immunity lasts considerably longer than first supposed (9), an observation of particular interest when it is compared with the general experience that an attack of diphtheria does not appear to confer any particular degree of immunity.

During the thirties, the incidence of diphtheria fell (Fig. 1), apart from a slight rise in 1935, to a minimum in 1940 of 860 cases, 44 of whom died. Thereafter, the incidence of diphtheria began to rise again to a maximum in 1944 with 3,353 recorded cases, 255 of whom died, a high lethality (approximately 10 per cent) and with a high incidence of croup. After this, at the end of the forties, there was an uninterrupted fall in incidence.

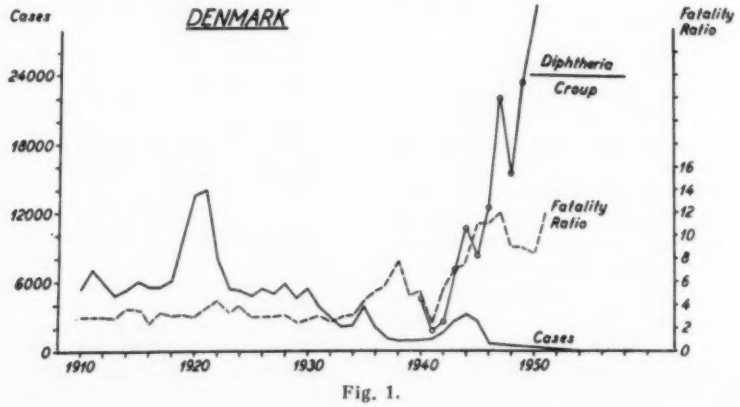

Fig. 1.

	Notified cases
1950	47
1951	25
1952	13
1953	9
1954	1
1955	1 (+ 1 doubtful)

At the Blegdamshospital no case has been admitted since 1950.

Now that diphtheria has practically disappeared from Denmark, the concept prevails that this is on account of immunization against diphtheria; but is this the only reason? If the course of diphtheria be followed both in Denmark and elsewhere, it is repeatedly found that epidemic waves are followed by troughs. In Denmark, this is clearly seen in 1865 and 1920 (Fig. 1). In Norway, only 72 cases were recorded in 1939 and in Sweden only 107 cases, which shows how low the incidence of diphtheria could fall without immunization.

The last great epidemic wave of diphtheria struck a number of European countries in addition to Denmark. On the basis of the official medical statistics from the various countries, the undulations in the incidence of diphtheria during the years 1940—1950 are shown logarithmically in Fig. 2. The Swedish curve practically co-

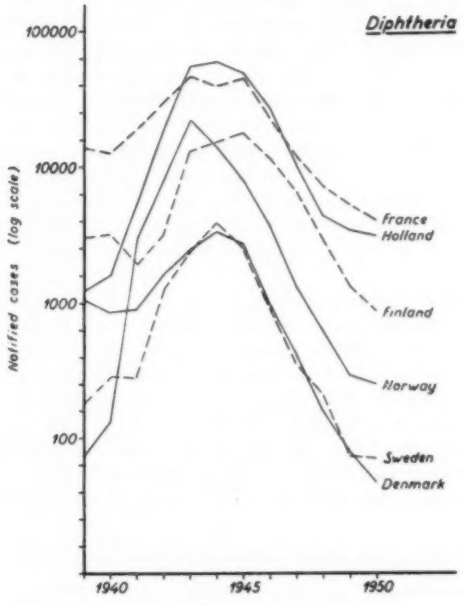

Fig. 2.

incides with that of Denmark and in 1954, although the population of Sweden is twice as large, only 1 case was recorded in Sweden and in Denmark respectively. This point is noteworthy when it is considered that in Sweden prophylactic immunization against diphtheria has been employed considerably less than in Denmark (9, 10, 11). In Norway, the incidence fell from a maximum of 22,732 cases in 1943 to 7 cases only in 1953, despite incomplete immunization. In Finland also, a large epidemic occurred with a maximum in 1945 and even in Iceland with its low diphtheria morbidity, this wave of diphtheria was in evidence with 11 cases in 1942 and 63 in 1943.

The rapid fall in the incidence of diphtheria which also occurred in Holland and France, has been attributed everywhere to the widespread immunization, stimulated by the malignancy of the epidemic. If, however, the uniform course of the epidemics in the various countries with their greatly varying percentages of immunization be reviewed, the correct conclusion to be drawn is that an epidemic wave of normal character had occured while the fall may have been more os less hastened by the immunization.

The state of affairs in England must be considered separately (Fig. 3). The incidence after

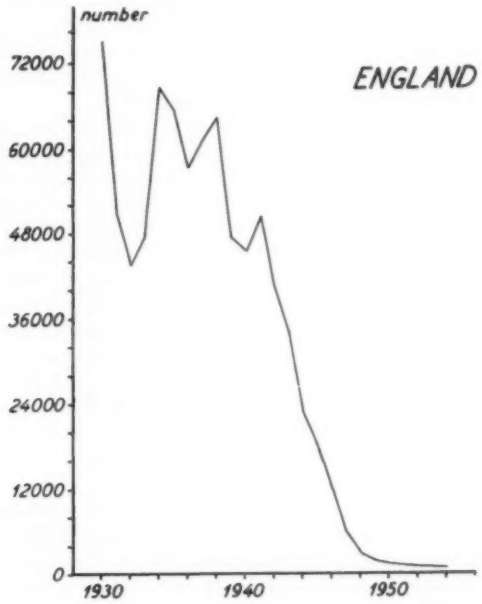

Fig. 3.

undulating between approximately 40,000 and 70,000 cases annually for many years, fell practically without interruption from 1938 until 1954 when 174 cases were recorded. Also in England this "dramatic fall", as it is called, is associated with the intensive immunization campaign which was started in 1942 (12, 13). The possibility cannot be entirely excluded that the fall from 64,937 cases in 1938 to 47,601 cases in 1939 might be the beginning of a spontaneous fall in the morbidity which may be mistaken for the striking result of immunization.

In an effort to prove the significance of im-

munization, the figures available have been used, in various places, in an uncritical manner. Thus, the conclusion was drawn from figures from Scotland (14) that the marked fall in the incidence of diphtheria between 1941 and 1949 was due to the fact that 70 per cent of all children under the age of 15 years had been immunized in 1941—42. In this instance, the co-incidence of diphtheria immunization and a spontaneous fall in the morbidity may be ignored. It is evident from the figures in Fig. 4 that among immunized cases, the incidence of diphtheria remained fairly constant until 1945 when there was a sudden fall, while among the non-immunized cases there was a constant steady fall even from 1941.

Fig. 4. *Scotland.*

Year	Reported cases		Deaths	
	o vacc.	+ vacc.	o vacc.	+ vacc.
1941	10,161	1,036	515	3
1942	6,956	1,799	279	11
1943	5,396	1,750	220	11
1944	4,378	1,774	179	4
1945	3,120	1,511	118	6
1946	2,122	1,024	85	6
1947	732	364	41	3
1948	521	202	30	1
1949	273	51	14	0

The March 1956 issue of the "Publications of the United Nations" (15) shows how confusing it may be when isolated figures are selected from an epidemic curve to prove the effect of a health measure. It is first remarked: "diphtheria antiserum was known already at the close of the nineteenth century and the incidence of diphtheria was successfully greatly reduced". Following this erroneous evaluation of the effect of diphtheria antiserum on the morbidity, the following figures from Norway are quoted as proof of the fall in the incidence of diphtheria following immunization:

1908: 555 deaths from diphtheria
1952: 6 " " "

but the picture is somewhat changed if one adds that in 1939, despite incomplete immunization, only 2 deaths occurred, while after a more extensive immunization campaign 747 deaths occurred in 1943.

If the same procedure were employed in the Danish material from the last epidemic (Fig. 1) it might well be maintained that the energetic immunization which was commenced in 1941—42 had been responsible for considerable rise both in the morbidity and lethality.

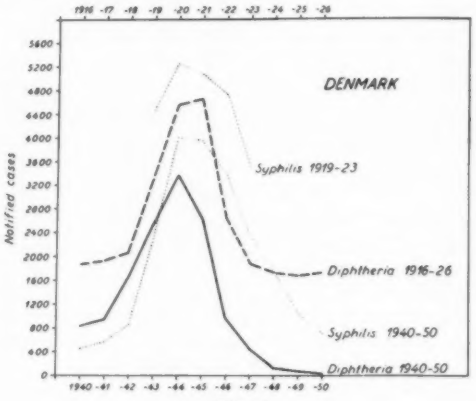

Fig. 5.

In Fig. 5, the Danish diphtheria curve from 1916 until 1926, *viz.*, long before the introduction of immunization, is shown for comparison. The general course of the curve resembles closely that of the curve from the forties with, however, the significant difference that it does not fall below the level of its commencement, whereas the curve from the forties falls as low as 1, far below its commencement. This difference may probably be attributed to immunization.

In Fig. 5, the curve for the cases of syphilis recorded in 1940—50 is also shown (this resembles closely the corresponding curve from Sweden) in order to demonstrate how an infectious disease with a completely different mode of infection from that of diphtheria has a similar rise and fall. The fall has been attributed to the introduction of penicillin, but the fact that the curve for the incidence of syphilis in 1919—23 shows a similar change has perhaps passed unnoticed.

The marked reduction in the morbidity of diphtheria in various parts of the world has been associated with *a change in the dominant type or group of bacteria.* The first investigations concerning the occurrence of the various groups in Denmark originates from T a r n o w s k i (16), who found that in the thirties the intermediate group was by far the most dominant while the gravis group was rare. This relationship changed

Table 1.

Degree of illness	Mild				Moderate				Severe				Deaths				Croup				Total		Mitis + gravis	
	mitis	%	gravis	%	mitis	%	gravis	%	mitis	%	gravis	%	mitis	%	gravis	%	mitis	%	gravis	%	mitis	gravis		
1945	116	56	78	35	74	35	89	40	17	8	55	24	13	6	30	13	5	2	9	13	207	222	429	4
1946	46	45	25	51	40	39	13	26	16	15	11	22	3	3	3	6	6	6	1	6	102	49	151	6
1947	16	34	12	63	23	50	4	21	7	15	3	15	3	6	3	15	4	8	2	15	46	19	65	7
1948/51	7	38	0	0	6	33	0	0	5	27	1		1	5	0	0	0	0	0	0	18	1	19	9
1945/51	185	49	115	39	143	38	106	36	45	12	70	24	20	5	36	12	15	4	12	12	373	291	664	3

entirely in the epidemic in the forties in which the gravis group became more prominent (17); the group had probably been introduced by the German army of occupation.

Following the investigation of 403 patients in the Blegdamshospital suffering from diphtheria during the period from October 1, 1943 to April 1, 1944, L a s s e n et alia (18) have dealt with the question of the different types or, perhaps more correctly, groups of diphtheria bacilli. These investigations were continued here on the basis of the case histories from Blegdamshospitalet after January 1, 1945.

Information corcerning the distribution is shown in Table 1.

The intermediate type was only demonstrated once. It will be noted that the percentage of mitis during the years 1945 to 1951 in the group of "mild" cases is falling but increasing in the "moderate" and "severe", that is, a shift in severity of this organism from the mild cases to the more serious cases. This shift is statistically significant. Correspondingly, a similar significant change is observed in the gravis from "severe" and "moderate" to "mild", i. e., with the years mitis has become relatively more serious while gravis, on the other hand, has become milder. Similarly, it is observed that the percentage of mitis cases among the total has risen from 1945 till 1951.

The distribution among the three groups of diphtheria bacilli is recorded in Fig. 6. These figures have been obtained partly from T a r n o w s k i's statements (16) and partly from the Diagnostic Department, the State Serum Institute.*) (18 a).

It will be seen in this figure that the intermediate type diminished during the beginning of the forties and had vanished entirely by 1947 while, on the other hand, both gravis and mitis which had shown a similar incidence since 1939, increased markedly from 1943 to reach a maximum in 1945 and thereafter fell just as rapidly and disappeared entirely.

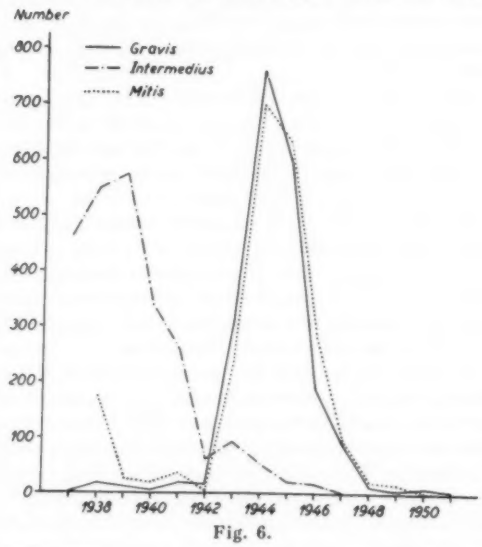

Fig. 6.

In England, also, (12) gravis and intermediate appear to be replaced by mitis:

	mitis	intermediate	gravis	indeterminate
1942	25%	29%	45%	1%
1948	51%	10%	24%	15%

As regards the *sex distribution of diphtheria*, Danish investigations (17, 18) have revealed the peculiarity that only approximately $^1/_3$ of the patients were males while $^2/_3$ were females.

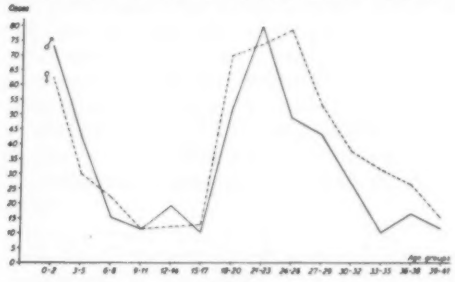

Fig. 7.

A review of the diphtheria patients in the Blegdamshospital from 1945 till 1955 (Fig. 7) reveals an excess morbidity for boys until the age of puberty when the sex incidence is equal, but thereafter a distinct excess morbidity is observed among women. Although the figures are small, these deviations in the sex distribution in the various age groups of the population of Copenhagen are sufficiently large to justify the conclusions mentioned above. These observations are supported, in addition, by statements from England and the figures from Vienna**) from 1943 till 1953, which are recorded in Fig. 8.

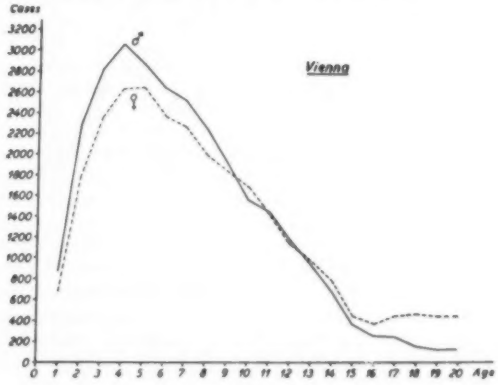

Fig. 8.

*) The author wishes to express his gratitude to Dr. J. S i i m, the State Serum Institute, who kindly put these figures at his disposal.

**) These figures were kindly placed at the author's disposal by Professor *H. Zischinsky*, Wilhelminenspital, Vienna.

This excess morbidity among women is frequently explained by the fact that in the home they are in closer contact with infectious children (17). It is, however, striking that this female excess morbidity which also holds true for scarlatina and rubella, is not encountered for example in measles, influenza and streptococcal throat infections (angina). Other determining factors must probably be present.

Age Displacement. As important evidence of the significance of immunization, both in Denmark and in England, displacement in the age group attacked has been recorded, since diphtheria, similarly to poliomyelitis and hepatitis, instead of being a disease of children, now attacks adults to an increasing extent. While no definite explanation is available as regards the two latter diseases, the cause in the case of diphtheria would appear to be the fact that immunization has primarily involved children. To probe the problem, the number of cases occurring during the years 1920—1950 in the gradually well immunized age-group 5—14 years is compared with the incidence in the incompletely immunized age-

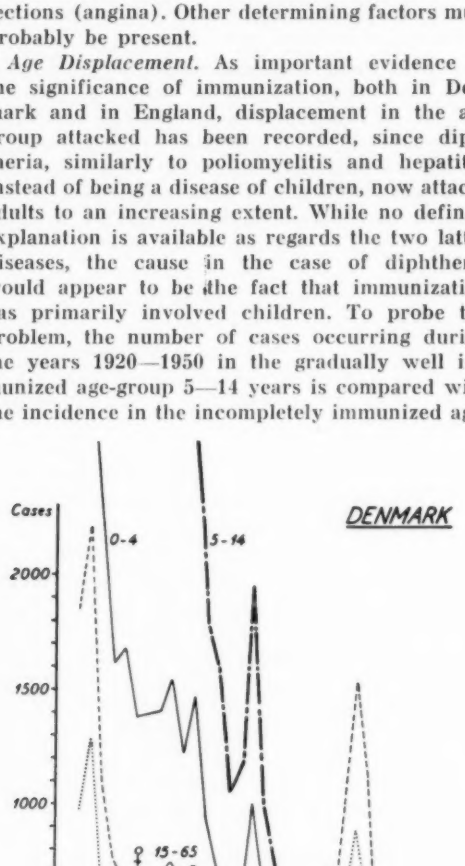

Fig. 9.

groups 15—65 years and 0—4 years. The figures originate from the Danish official medical statistics (Fig. 9). It appears from these figures that while the age incidence is practically equal until 1942 when immunization of children came into full swing, they thereafter separate so that adults form the peak of the epidemic wave in 1944, while the incidence in the age-group 0—4 years only rises very slightly and after 1945 coincides with the other age-groups. The same state of affairs, but expressed as percentages, is shown in Fig. 10.

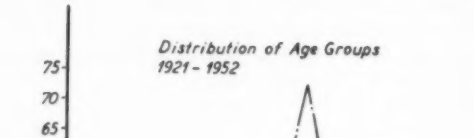

Fig. 10.

The fraction which the age-group 5—14 years constitutes out of the total number of cases recorded falls rapidly during the years round about 1942 from approximately 50 per cent to the lowest value of approximately 13 per cent about 1945, after which it rises slightly. Simultaneously, the fraction constituting the age-group 15—64 years rises from 20 per cent to a maximum of 72 per cent about 1945, after which time it falls again. These figures provide good evidence that immunization has caused the difference. Immunization has not been able to alter the configuration of the epidemic wave which depends upon non-immunized individuals, but it has probably played a decisive rôle in reducing the incidence which now has fallen to 1.

The change to predominance of the adult age group over the children's group is first noticeable in 1943. This displacement from children to adults is also encountered in other countries such as Norway (19) and U. S. A. (20).

Immunity. The data on cases from after 1944 confirm entirely the statements of L a s s e n et al. (18). The majority of the patients were not immunized; only a few of those attacked were adequately immunized. None of the 5 fatal cases proved to be adequately immunized.

A good illustration of the significance of immunization is provided by a small epidemic which occurred in East Bornholm in 1951. There, two elderly non-immunized individuals died from diphtheria. They infected a neighbouring family in which a man aged 31 years developed diphtheria but recovered, while the other 5 members of the family became chronic carriers. None of them had been immunized and the gravis group was demonstrated in all. A non-immunized boy of 7 years became infected from the latter family

and died, while an incompletely immunized boy developed mild diphtheria, and their mother, who was not immunized, became a carrier, all with the gravis group. In the same district, but without demonstrable contact with the cases mentioned above, a man aged 34 years died in November 1955 following an illness which resembled diphtheria and the legal autopsy showed typical myocarditis. Examination for the presence of diphtheria bacilli was not undertaken, but comprehensive swabbing from the contacts showed that a brother-in-law who had been immunized in 1946 was a carrier (gravis).

This shows that also in periods when diphtheria seems practically to have disappeared, small foci of malignant infection may persist. This should be a stimulus not to diminish the efforts to maintain thorough immunization of the population of the country.

Carriers. Very little is known about diphtheria carriers in Denmark at present. Probably the number concerned is limited as no cases have been found in the past two years either in the State Serum Institute in Copenhagen nor in The Diagnostic Station in Aarhus in Jutland (N ø r b y (21)). It was feared that immunization would produce healthy carriers, but this fear, as it appears from experience in England, is unfounded. On the other hand, the absence of carriers suggests that there is no possibility of maintaining latent immunization by such carries.

Although there appear to be few or perhaps no carriers of diphtheria bacilli in Denmark, a danger still exists in not having a completely immunized population, *viz.*, a constant risk of the introduction of diphtheria from abroad. The course of the epidemic wave of diphtheria in the forties (Figure 2) shows that following a calm period, the incidence of diphtheria rose markedly in the majority of European countries. This phenomenon has been associated with the invasion by German troops, as at the commencement of the forties a severe epidemic of diphtheria occurred in Germany (245,067 cases in 1943). This holds true for Denmark, Norway, Finland, Holland, Belgium and France. In Sweden, where the course of the epidemic resembles that in Denmark to a surprising degree, this was attributed to the Finnish refugees.

Although the incidence of diphtheria in the majority of European countries is once more in the trough of a wave, and it is to be hoped, can be kept there by the extensive immunization campaign which has been initiated in recent years, the fact cannot be ignored that in numerous places, both in Europe and elsewhere, diphtheria still occurs (23) and may be rapidly spread by modern means of communication.

CONCLUSION

The marked fall in the incidence of diphtheria following the epidemic in 1942—46 was not entirely due to immunization against diphtheria but also to the natural fall of the epidemic wave.

Whereas diphtheria was previously primarily a disease of children, it has now become a disease of adult life. This is due to the immunization of children. The crucial point was attained in 1942.

The intermediate group of the diphtheria bacilli, which was the dominating group in the thirties, was replaced in the forties by the gravis and mitis groups. The gravis group appears now to be giving way to the mitis group. The latter may produce not only slight but also severe, fatal and croupous cases.

An excess morbidity exists for boys until the age of 6—7 years; no difference is demonstrable at puberty; thereafter, an increasing excess morbidity is noticeable in women.

No deaths have occurred in the Blegdamshospital in adequately immunized patients since 1945.

Although diphtheria has, at present, disappeared from Denmark, immunization must be maintained to the full extent on account of the risk of the introduction of malignant bacilli from abroad.

Serum therapy was instituted in 1895 during a rapid fall in the lethality from diphtheria, while immunization was started at the peak of the great epidemic wave of diphtheria in the middle of the forties. In both situations, these coincidences were the cause of incorrect evaluation in the question of "post or propter".

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B. C. G. VACCINATION OF THE NEWBORN

By FOLKE TUDVAD, J. KRINGELBACH and K. BIERING-SØRENSEN

Although B. C. G. vaccination has now been employed for a number of years, and steadily increasing numbers are being vaccinated against tuberculosis, it can hardly be said that the most suitable time for the vaccination has been established.

As a first consideration, the post-natal period has the great advantage that the infant, at that period, could only have been exposed to tuberculous infection in extremely rare instances, so that a prior observation period can be avoided, and at the same time the earliest possible protection can be obtained precisely in that period when tuberculosis offers the greatest risk of serious complications.

On the other hand, consideration must be given to the question of whether vaccination during the post-natal period is as effective as a vaccination at a later period, to whether the number of complications will be greater, and finally to whether vaccination of the newborn has an effect on the growth of the infant.

Opinion has been strongly divided on the question of the effectivity of B. C. G. vaccination of the newborn, in that various authors (1, 4—5, 7—9, 11, 13—19, 21—22) have found the number of tuberculin-positives to vary between approx. 60 % to close up to 100 %. These various investigations, however, are not directly comparable, as various methods have been employed and different quantities of vaccine used. Some authors (5, 20) state that it takes longer than usual for newborn infants who have been vaccinated to become tuberculin-positive, just as it is claimed (9, 20) that newborn infants whose mothers have tuberculosis have greater difficulty, and take longer in being tuberculin-positive, than infants whose mothers do not have tuberculosis.

Only a few statements regarding the risk of complications in B. C. G. vaccination of the newborn are available. Biering-Sørensen (3) found 3.5 % with abscesses among approx. 4,000 vaccinated newborn infants. Guld et al. (6) found 6.3 % with glandular abscesses among 143 cases who had been vaccinated as newborn infants with a quantity of vaccine of 0.075 mg, but found 16.5 % abscesses if twice the quantity of vaccine was given, and 3.2 % if half the amount of vaccine was given. Øster (24) found only 0.5 % of cases of complications among infants vaccinated during the first year of life. As a result of a follow-up of infants vaccinated during the period 1942—1947 at the Copenhagen Municipal Central Tuberculosis Dispensary, 0.5 % were found to have abscesses (quoted from 3). In the case of older children, Holm (10) found only 1 abscess among 4349 vaccinated school-children, and Winge (23) found 0.9 % with abscesses among 1508 children vaccinated against tuberculosis.

The question of the progress of the children after B. C. G. vaccination has apparently not interested very many. It has been presumed (2) that satisfactory progress can come to a stop after the vaccination, and an investigation by Gyllenswärd (8) might suggest that this is correct, in that a comparison between the weights of 108 cases of B. C. G. vaccinated (77 vaccinated between 0 and 16 days after birth) and 114 non-vaccinated infants of the same age, showed parallel weight curves for the first weeks, but thereafter, till around 7 months of age, a smaller weight increase for the vaccinated group. After the age of 7 months the vaccinated cases increased in weight more than the non-vaccinated.

On the other hand, Larsen & Bastrup-Madsen (12) found no difference in weight increase from birth till 4, 8 and 12 weeks of age between 2 groups of newborn infants; one group, with 22 infants, was vaccinated shortly after birth, while the other group consisted of 100 non-vaccinated newborn infants. According to the figures put forward by the authors, it appears that the B. C. G. vaccinated infants, if anything, put on more weight than the non-vaccinated.*)

However, the data put forward in both cases (8, 12) were collected irregularly over a period of 7—8 years, originated from Children's Homes, and, finally, the infants were vaccinated on account of exposure to tuberculosis.

The present investigation has therefore been carried out to investigate whether newborn infants, vaccinated with Danish B. C. G. vaccine in the usually recommended dose, and who are being looked after at home,

1) become tuberculin-positive with the same frequency as older children and adults,
2) thereafter develop complications in greater number than is found among older children and adults,
3) are affected in their growth by the B. C. G. vaccination.

MATERIAL

From the 1st of January, 1950, and throughout the course of that year, all mothers delivered at the Municipal Maternity Hospital, Martinsvej,

From the Children's Hospital, Martinsvej, Copenhagen Municipal Maternity Hospital, Martinsvej, and Copenhagen Municipal Public Health Nurses Agency.

*) In a recent work Gaisford (Brit. Med. J. 1955, 2: 1164) using Danish B.C.G. vaccine, found no slowing in the weight gain in vaccinated infants.

were invited to have their newborn infants B. C. G. vaccinated, unless they were ill or premature.

Generally speaking, the mothers belonged economically and socially to the middle class, and it was seemingly a matter of chance as to who accepted the offer of vaccination and who refused it.

In this manner it was possible to vaccinate a series of infants in the post-natal period, and, for the purpose of comparison, obtain another, smaller group of infants, born at the same time and from the same social level.

The infants vaccinated received 0.1 ml B. C. G. vaccine intracutaneously in each deltoid region (0.075 mg × 2) 3—5 days after birth, without previous X-ray control or tuberculin test. The vaccination was carried out by doctors from the Children's Hospital, Martinsvej. The mothers were requested to attend the hospital with their infants about 2 months later, to check for Moro-reaction and possible complications. If they did not attend, information was sought on these points, partly by writing to the mothers, partly by examining the records of the Public Health Nurses, and partly from the hospitals in those cases where the infants had been admitted later.

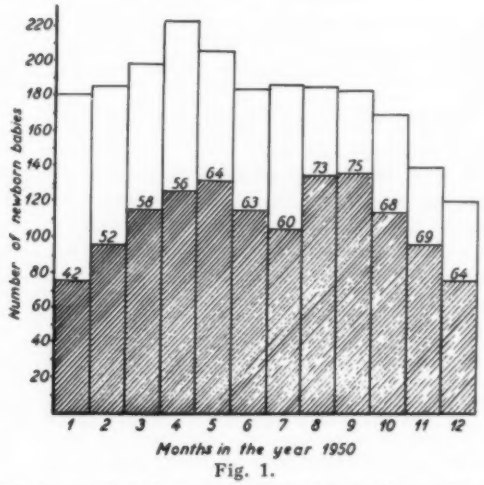

Fig. 1.

Number of B. C. G. vaccinated (hatched columns) and non-vaccinated (unhatched columns) cases in the individual months of 1950. The figures above the hatched columns indicate the percentage of cases vaccinated in the month in question.

In all, 1330 newborn infants were vaccinated (61.3 %) during the course of 1950, while 829 (38.7 %) were not vaccinated. Fig. 1 shows the distribution of vaccinated and non-vaccinated within the 12 months of the year. 51.7 % of the vaccinated and 52.1 % of the non-vaccinated were boys.

THE MORO-REACTION AFTER VACCINATION

Of the 1330 vaccinated, 710 (53.3 %) appeared at the hospital approximately 2 months after vaccination and had their Moro-reaction read. 5 (0.7 %) were found negative. It was possible to collect information on the More-reaction in a further 489(36.8 %), of which 6 were recorded as being More-negative. We thus have information on the More-reaction of 1199 of the vaccinated cases in all, of which 11 (0.9 %) are negative.

FREQUENCY OF COMPLICATIONS

Among the 710 who were followed-up at the maternity hospital, the following complications were found approximately 2 months after the vaccination:

Local ulceration > 5 mm in	45 (6.3 %)
Glandular abscess in	17 (2.4 %)
Adenitis in	81 (11.4 %)

However, there is no doubt that complications can arise at a period later than 2 months after the vaccination, especially in the form of adenitis and glandular abscesses.

We have, therefore, gone through the records of the Public Health Nurses for all the vaccinated cases visited, in all 1199. In this survey of the records we have only paid attention to abscesses, since an assessment of the number of cases of adenitis cannot be expected to give an even approximately correct figure, for the nurses were not instructed beforehand to feel for the glands. On the other hand, it may be assumed that the abscesses have been noted in the nurses' records. Furthermore, in the cases where the infants have been admitted to hospital, we have sought information from the hospitals on possible swollen glands and abscesses.

Of the 1199 vaccinated, 33 (2.75 %) in all developed abscesses within 1 year of vaccination.

This is a relatively large number of abscesses in relation to the number quoted as developing after the vaccination of older children. If the distribution of the number of abscesses in relation to the separate months of the year is examined (Table 1), it would appear as if vaccination during the summer months gives the least number of abscesses.

Table 1.
Number of glandular B. C. G. abscesses in relation to time of year.

Month in 1950	Number of vaccinations	Glandular abscesses Number	in %
January	68	7	10.3
February	89	3	3.0
March	110	3	2.7
April	116	6	5.2
May	116	4	3.4
June	103	0	0
July	104	2	1.9
August	124	0	0
September	121	2	1.8
October	102	1	1.0
November	81	2	2.5
December	65	3	4.6
Total	1199	33	2.75

PROGRESS IN WEIGHT

Since the only measurable criterion for the progress of the infants which we have had available is their weight, we have gone through all the Public Health Nurses' records for infant born in the Maternity Hospital, Martinsvej, in 1950. A number of these records were excluded, namely, the records for

1) all premature babies,
2) all infants where one or more of the weights at 1, 2, 4 and 6 months are lacking,
3) all infants who have been hospitalized or have had serious illness at home,
4) all infants who have been in a day nursery or similar institution within the first six months of life,
5) twins,
6) infants in the control group, who were B.C.G. vaccinated later,
7) infants in the vaccinated group who did not become Moro-positive, as well as infants in cases where information on the Moro-reaction was lacking.

Thereafter remain 1297 infants who enter into the following calculations*), of these there are 855 (65.9 %) who were vaccinated as newborn infants, while 442 (34.1 %) are unvaccinated.

Table 2.
The average weight increase per day for vaccinated and non-vaccinated infants.

	Average weight increase per day	
	Vaccinated	Non-vaccinated
1st month of life	21.1 g	19.9 g
2nd month of life	30.2 g	31.0 g
3rd + 4th month of life	25.9 g	26.4 g
5th + 6th month of life	21.4 g	22.0 g
Number of children	855	442

However, as the infants were not weighed at precisely the same age intervals, calculations of the averages for the weights found in the two groups cannot be made. It was therefore decided instead to calculate the weight increase per day for each infant, for the first, second, third + fourth and fifth + sixth months of life.

Table 2 shows the average weight increase per day for vaccinated and non-vaccinated, set out for the 4 age groups. There is a very slight tendency for the weight increase in the vaccinated infants to be a little less than in the non-vaccinated infants for the period from 2—6 months. The differences, however, are no greater than that they could be explained by chance.

There is the further possibility that the 2 groups: vaccinated and non-vaccinated, have not been uniformly nourished, and that progress has therefore not been uniform, just as one cannot ignore the possibility that unsatisfactory progress has led to extra measures regarding nourishment, for example earlier bottle freeding and puréed foods as supplements.

In Table 3, therefore, a corresponding average calculation of the weight increase per day has been carried out for vaccinated and non-vaccinated infants who have had breast-feeding exclusively for at least 4 months.

Table 3.
The average weight increase per day for vaccinated and non-vaccinated infants, who have had breast feeding exclusively for at least 4 months.

	Average weight increase per day	
	Vaccinated	Non-vaccinated
1st month of life	23.5 g	23.2 g
2nd month of life	31.7 g	32.3 g
3rd + 4th month of life	23.2 g	22.8 g
5th + 6th month of life	19.1 g	18.6 g
Number of children	308	144

The figures in Table 3 seem to indicate rather the opposite tendency to those of Table 2, in that the vaccinated infants have had a little greater weight increase per day than the non-vaccinated infants, with the exception of the 2nd month of life.

There is the further possibility that the distribution of boys and girls is not uniform, and that this can have an influence on the calculated average weights. In Table 4, therefore, the material of Table 3 is distributed according to sex. It will be seen that the average weight increase per day for the girls is a little less than for the boys, but the tendency for both boys and girls is the same as in Table 3.

Table 4.
The average weight increase per day for vaccinated and non-vaccinated infants, who have had breast feeding exclusively for at least 4 months, distributed according to sex.

	Average weight increase per day	
	Vaccinated	Non-vaccinated
Boys		
1st month of life	24.2 g	24.3 g
2nd month of life	33.5 g	34.1 g
3rd + 4th month of life	23.9 g	23.2 g
5th + 6th month of life	19.0 g	18.9 g
Number of boys	158	74
Girls		
1st month of life	22.9 g	22.0 g
2nd month of life	29.8 g	30.5 g
3rd + 4th month of life	22.4 g	22.4 g
5th + 6th month of lift	19.2 g	18.3 g
Number of girls	150	70

*) The calculations in what follows have been carried out by T. Feldvoss, M. A. (Econ.), Copenhagen Municipal Statistical Department, to whom our best thanks are due for the extensive work involved.

Finally, in Fig. 2, the number of vaccinated and non-vaccinated infants who have had exclusively breast-feeding for at least 4 months is set out as a percentage distribution into weight groups according to their weights at approximately 6 months of age. The distribution in the 2 groups is quite uniform.

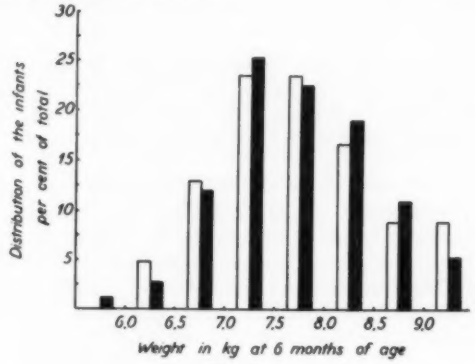

Fig. 2.

Infants who have had breast feeding exclusively for at least 4 months, distributed in percentage according to weight at the age of 6 months. The open columns indicate the non-vaccinated infants, the black columns those infants B.C.G. vaccinated at birth.

Thus, it appears that no difference is demonstrable in the weight gained during the first half year of life between infants who have been B.C.G. vaccinated at birth, and infants who were not so vaccinated.

DISCUSSION AND CONCLUSION

As a result of the follow-up described here of infants who were B.C.G. vaccinated when newborn, it is demonstrated:

1) That these infants are More-positive approximately 2 months after the vaccination in approximately 99 % of the cases. The frequency of taking is thus of the same order of magnitude as with older children and adults.
2) That the frequency of complications in the form of glandular abscesses is greater (in this material 2.75 %) than among older children.
3) That the B.C.G. vaccination of the newborn does not affect the progress of the infants during the first half year of life.

There still remains the question as to whether infants, vaccinated when newborn remain the tuberculin-positive as long as infant who are vaccinated at a later date. This question cannot be answered by the material here. Rosenthal (17) states that 74 % of vaccinated newborn infants are positive after 40—45 months, Wasz-Höckert (22) found that 70 % of infants vaccinated in the age of 0—2 months were positive 6 years later, and Black (4) states that 80 % of newborn infants vaccinated are positive 6—6½ years later.

If these statements hold, and if the risk of complications could be reduced, for example by giving lesser quantities of vaccine than those used here (6), the B.C.G. vaccination of newborn infants can continue to be recommended, even though infant vaccination is technically more difficult than that of older children, and should perhaps for this reason be restricted to specially trained vaccinators.

SUMMARY

All newborn infants at the Maternity Hospital, Martinsvej, had the opportunity of being B.C.G. vaccinated in the course of the year 1950. Out of 2159 newborn infants, the mothers of 1300 (61.3 %) accepted the offer.

It was possible to collect information on the Moro-reaction of 1199 (90.1 %) out of these 1330: among these there were 11 (0.9 %) who had not become Moro-positive.

On follow-up at the Maternity Hospital, and by going through the Public Health Nurses' records, it was found that 33 (2.75 %) had developed glandular abscesses after the vaccination.

On the basis of the weights of the infants visited at their homes by the nurses, a calculation has been made of the weight increase per day during the 1st, 2nd, 3rd + 4th and 5th + 6th months of life for the above. No indication can be found that the B.C.G vaccination of infants during the post-natal period affects their progress during the first six months of life.

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MENINGITIS DUE TO ESCHERICHIA COLI

REPORT OF 25 CASES IN NEWBORN INFANTS

By ERIK F. MOGENSEN, AGNETE JENSEN and OTTO STEFFENSEN

In 1885, Th. Escherich described the Bacterium coli, which he conceived as a saprophyte. However, it soon became clear that the organism may be pathogenic for man, and as early as 1892 Macaigne (7) was able to collect five cases of meningitis caused by Esch. coli from the literature. Since then a large number of single cases have been published; in 1942, Barret et al. (2) reviewed a total of 108 cases from the literature. Even though Bact. coli meningitis may occur in adult life, the disease has its highest incidence in children, particularly during the first few years of life. That Esch. coli has a special pathogenicity for the infant organism is also seen in veterinary medicine, in which Bact. coli sepsis is well known in young calves (4).

It is difficult to say anything definite of the frequency with which Bact. coli meningitis occurs. Within three years, Randall (8) found six cases in Guy's Hospital in London. Haworth (6) observed five cases of Bact. coli meningitis among 50 children with purulent meningitis admitted to Alder Hey Children's Hospital in Liverpool. Smith (9) found 19 cases of this type of meningitis among 344 infants and children with purulent meningitis.

In Denmark, the first case of Bact. coli meningitis was published by Bojlén (3) in 1937; since then one case has been described by Winge Flensborg (5) and seven by Dupont and Thamdrup (10).

MATERIAL

The present series was collected in 1955 from all paediatric departments in Denmark, to which we applied for the loan of the case records of all cases of Bact. coli meningitis occurring during the last 10 years. By this method we succeeded in tracing 24 cases*).

One department informed us that they wanted to publish their own cases. Professor H. C. A. Lassen placed an additional case at our disposal. Our series then comprises 25 cases, including four from this department, and is thus the largest series of Bact. coli meningitis so far published. All the cases included were confirmed by bacteriological studies on the spinal fluid.

*) We are indebted to the heads of the departments concerned for their kind permission to make use of the case records for the purpose of this publication.

From the Paediatric University Clinic (Chief: Professor *Bent Andersen*), the Municipal Hospital, Aarhus, Denmark.

AGE AND SEX DISTRIBUTION

It appears from the literature that Bact. coli meningitis principally occurs in young infants. Thus, among the 19 cases published by Smith (9), the disease occurred within the first month of life in 13. The same age distribution was revealed in our own series (Table 1).

Table 1.
Age distribution of 25 patients with Bact. coli meningitis.

Age at first symptom	1st day	2nd-7th day	2nd week	6th week	Total
No. of patients	8	10	5	2	25

It should be noted that in some cases it was difficult to determine the exact time of the onset of the first symptoms, for which reason the figures in Table 1 must be taken with some reservation. It is seen that all the patients were less than 6 weeks old at the onset of the disease. The series consisted of 9 girls and 16 boys. Other writers have also disclosed a male preponderance among their patients. Thus, Randall had five boys among his six cases. However, the sex distribution is rarely stated in the series reported.

BIRTH HISTORY

In a disease with such an age distribution it will be reasonable to investigate if features of the birth history may be suspected of being of importance in the development of the disease. Of the 25 patients in our series, 24 had been born in maternity homes or hospitals; this is a remarkably high figure, as only 33 per cent of all children in this country are born in institutions; in Copenhagen, however, it is 80 per cent. The cause of this finding is unknown, but may possibly be attributed to the high frequency of difficult births in the series.

The details of the birth history are known in the 24 cases in which the infants were born in maternity homes or hospitals. Among these 24 infants, six were delivered by forceps and labour was unduly protracted in three cases, so that a total of nine of these 24 deliveries must be described as pathological. In addition to three of

the nine infants just described, three others were asphyxiated at birth. Three of the infants were born prematurely (birth weight less than 2500 g). Thus, only nine of the 24 deliveries were normal, occurring at the expected date of confinement. That is to say that the children in this series from the very start of life were heavily handicapped as compared with the average newborn infant in Denmark. The relation between this finding and the Bact. coli infection is rather obscure. The enfeebled infants may have had a lowered resistance to the infecting organism, or they may have been exposed to massive infection with Bact. coli during the manipulations involved in the delivery. In several cases it has been rendered likely that the mother was the source of infection, since the same strain of Bact. coli was isolated from her (10).

In four of the 25 cases, a varying degree of umbilical infection was described in the case records, so that the meningitis may be referable to this condition in some cases. Bacterial studies on material from the infected umbilicus had not been carried out in any of the cases. In most case records, no special mention was made of the umbilicus.

Other authors have found that Bact. coli meningitis occurs especially in infants with obstructive anomalies of the urinary tract or spina bifida (1). None of these anomalies were encountered in our series. In the patients who succumbed, the urinary tract was studied at autopsy in all cases except one.

SYMPTOMS

As in other forms of meningitis in infancy, the usual clinical manifestations of meningitis were either inconspicuous or completely absent. The classical picture with fever and increased tension of the anterior fontanelle was present only in exceptional cases, and stiffness of the neck was never encountered. Only six of the 25 patients had fever before the diagnosis was made. In three infants, convulsions suggested that they were suffering from a lesion of the central nervous system. In most cases the cardinal symptoms were general debility and refusal of feedings. In two cases the conspicuous symptoms were vomiting, cyanosis and respiratory distress. In reviewing the case records we did not succeed in disclosing a single symptom which by its character and frequency can be used as a clue to the diagnosis. In most cases of the series, lumbar puncture was carried out because of a suspicion of some other intracranial disease (e. g., haemorrhage), so that the diagnosis of meningitis came as a surprise. This is illustrated by the following case history.

CASE HISTORY

A girl, aged 1 month, was admitted to this hospital (Dept. A, 212/55). The delivery had been normal; the infant was not asphyxiated; birth weight 3,850 g. During the first few days of life the infant began to refuse the breast, became rapidly tired of sucking and failed to thrive. In addition, the infant became startled and stiff when touched. On the eighth day of life a fever developed; penicillin was then given for two days, but as the fever persisted, she was given sulphonamide at the age of two weeks, following which the temperature returned to normal. She was then well for a few days, but on the 22nd day of life a seizure of clonic convulsion and opisthotonos suddenly developed, for which reason the patient was transferred to the Department of Neurology, Aarhus Municipal Hospital, a week later. On admission here, the temperature was normal, but the infant was weak and limp, with a tendency to opisthotonos. There was no abnormal bulging of the anterior fontanelle. Occasional convulsive seizures continued in spite of administration of phenobarbital. On the third day after admission subdural puncture was performed because a subdural haematoma was suspected. As no haematoma was disclosed, the ventricular system was punctured, and a yellowish milky fluid was evacuated. Cell count 40,000/3 per c.mm; the albumin and globulin content was pathologically increased (Bisgaard). Culture of ventricular fluid yielded growth of Bact. coli. The patient was then transferred to the Paediatric University Clinic, where oral treatment with sulphonamide and oxytetracycline was given. Six days later the spinal fluid was sterile, and the patient was returned to a local hospital. The infant was later examined in the Department of Neurosurgery at the age of 3 months; motor development was retarded, and the infant was unable to raise the head when placed in the prone position. Ventriculography revealed porencephalia.

Owing to this lack of typical signs, lumbar puncture should not be postponed in infants with unexplained and uncharacteristic debility during the first few weeks of life. A definite diagnosis is possible only by this procedure, which should be performed with a suitably coarse needle, as it may be difficult to evacuate the markedly purulent spinal fluid. If lumbar puncture fails, ventricular puncture should be performed. As in other forms of meningitis, it is of the greatest importance that a bacteriological diagnosis is secured at the earliest possible time.

PROGNOSIS

That early diagnosis is really important appears from Table 2, in which the prognosis is related to the time of diagnosis after the onset of the disease. As already mentioned, the figures should be taken with some reservation, since it was often

Table 2.

The prognosis as related to the time of diagnosis after the onset of symptoms.

Course of disease	No. of patients	Time of diagnosis after onset of initial symptom, in days	
		Average	Range
Recovered	6	2.1	1— 7
Survived with defects ..	6	8.1	1—29
Primary deaths	13	8.8	1—19
Total	25		

difficult to ascertain the exact time of the onset of the first symptoms.

It is seen that six patients were completely cured of their meningitis. Of these, five were followed up 3 to 18 months after discharge; one was not seen later, but he was completely well and alert when discharged at the age of six weeks. Six patients survived with defects. They were re-examined a few months after discharge. In all six motor development was retarded. Hydrocephalus was revealed in four, and one of these died later. Ventriculography showed porencephalia in one. One patient had mild paresis of the right hand and appeared to be mentally retarded when seen at the age of six months.

Primary death from meningitis occurred in 13 cases. Four patients died after a few days' illness; three were ill for up to one month, while death ensued after more than one month in six. It is seen from the table that the diagnosis was made and treatment instituted appreciably earlier in the patients who recovered completely than in those who died or survived with defects. The prognosis of meningitis due to Esch. coli is poor, but although the figures in Table 3 are too small for definite conclusions, they suggest that an appreciable improvement has occurred in the outlook during recent years.

Table 3.

The prognosis as related to the time of occurrence of the meningitis.

Course of disease	1946-1950	1951-1954 + first 3 months of 1955	Total
Recovered	0	6	6
Survived with defects ..	1	5	6
Primary deaths	4	9	13
Total	5	20	25

TREATMENT

According to Table 3 the percentage of cure has increased from zero to 30 per cent during the period under consideration. The improved prognosis is due to several factors; it is now possible to make the diagnosis at an early phase of the disease, and more efficacious remedies are at our disposal in its treatment. It is impossible to say anything definite of the effect of the various antibiotics on the basis of the results of the present analysis. The patients were treated in different hospitals, and in nearly all cases several drugs were used, either simultaneously or successively. However, we are under the impression that streptomycin is superior to all other antibiotics in the treatment of meningitis due to Esch. coli. All the survivors except one were given streptomycin, while only seven of the patients who died had received this drug. However, the most rational treatment must be to give streptomycin in combination with tetracycline antibiotics or chloramphenicol. Intrathecal injection of the drug used was employed only in two cases; both patients died, but we dare not draw any conclusion from this.

An analysis of the series with a view to a possible relationship between obstetrical complications and the subsequent course did not reveal any correlation. Of the patients who recovered, three were boys and three girls. During the collection of the case material we were struck by the fact that some paediatric departments had a relatively large number of cases of Bact. coli meningitis, while others had no cases at all during the 10-year period. This can scarcely be traced back to a difference in the number and types of patients, but may suggest that not all cases of this type of meningitis are diagnosed. One of the purposes of this study has been to call attention to the disease in the hope that this may contribute to a more frequent and earlier diagnosis of Bact. coli meningitis, which is conducive to the relatively high infant mortality which still prevails during the first month of life.

SUMMARY

Twenty-five cases of meningitis due to Esch. coli in young infants collected from all paediatric departments in Denmark are surveyed. A strikingly large number of the cases occurred after obstetrical complications. The difficulties in diagnosis are emphasized, and the prognosis, which is still poor, is discussed.

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